Sporadic schwannomas and neurofibromas

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Introduction

This article includes discussion of sporadic schwannomas and neurofibromas, chitoneuroma, neurilemmoma, perineural fibroblastoma, abducens schwannoma, facial schwannoma, hypoglossal schwannoma, jugular foramen schwannoma, malignant schwannoma, neurofibroma, neurofibrosarcoma, peripheral nerve schwannoma, schwannoma, spinal schwannoma, sporadic neurofibromas, sporadic schwannomas, and trigeminal schwannoma. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

In this article, the author provides an in-depth review of the pathology, biology, clinical presentation, and treatment options for sporadic schwannomas and neurofibromas. These tumors arise from the nerve sheaths of cranial nerves, nerve roots, spinal nerves, and peripheral nerves. The most common location for schwannomas is the eighth cranial nerve, whereas neurofibromas more commonly arise along the spinal nerve roots. Maximal surgical resection is the treatment of choice for most tumors. Radiotherapy is only used in selected cases. Chemotherapy is still under investigation for therapeutic potential. In this update, the author reviews advances in the molecular biology and therapeutic approaches to these tumors.

Key points

- Schwannomas are slow-growing extra-axial tumors that can arise from any cranial nerve or spinal nerve root. They most commonly arise from the eighth cranial nerve.
- Surgical resection is the treatment option of choice for most tumors. Complete resection can result in a surgical cure.
- In selected cases, radiosurgery may be as effective as surgery at local control of tumor growth.
- Chemotherapy is not applicable to most schwannomas. Data suggest that anti-angiogenic treatment approaches may be helpful in selected cases.

Historical note and terminology

By most accounts, the earliest reported description of a vestibular schwannoma was by Sandifort, in 1777 (Sandifort 1777). The first clinicopathologic correlation was by Leveque-Lasource in 1810 (Leveque-Lasource 1810). The earliest complete clinical report of a patient with a vestibular schwannoma was by Bell in 1830, as described by Cushing (Cushing 1917). In 1835, Cruveilhier is credited with the most complete description of both the clinical and pathologic features of the tumor (Cruveilhier 1835). The first successful operative removal of a vestibular schwannoma was by Sir Charles Balance in 1894. Based on the clinical description and autopsy findings of a patient with a vestibular schwannoma that was localized and diagnosed antemortem, Von Monakow was of the opinion that patients with these tumors were excellent surgical candidates (Von Monakow 1900). This report generated much interest within the neurosurgical community in surgical therapy for vestibular schwannomas. Over the next 30 years, surgical techniques and approaches to intracranial schwannomas were refined to such a degree that operative mortality was reduced from approximately 50% to 60% in the early 1900s to 4% by 1931 (Macfarlane and King 1995). New techniques introduced by Cushing (eg, subtotal tumor removal, decompressive suboccipital craniectomy, uncapping of the cerebellum) were responsible for much of this improvement. Further refinement in surgical techniques, the use of intraoperative monitoring, and the advent of CT and MRI have further improved surgical morbidity and mortality over the last 30 years.

Clinical manifestations

Presentation and course

As tumors of peripheral nerve sheath origin, sporadic schwannomas and neurofibromas can originate from cranial

nerves, spinal nerves or nerve roots, or peripheral nerves. Therefore, the clinical evolution and manifestations are variable, depending on the location and rate of growth of the tumor.

Schwannomas. Schwannomas make up 6% to 8% of all primary brain tumors, and 10% to 30% of all primary spinal cord tumors (Newton 1994; Newton et al 1995; Seppala et al 1995b). They usually present as solitary, sporadic tumors, unassociated with predisposing conditions such as neurofibromatosis type 1 or neurofibromatosis type 2. In particular, only 5% of acoustic schwannomas are diagnosed in patients with neurofibromatosis type 1 or neurofibromatosis type 2. There is a predilection for schwannomas to affect sensory roots more than motor or autonomic branches. In most series, females are affected slightly more often than males. Within the intracranial cavity, greater than 85% to 90% of schwannomas affect cranial nerve VIII, 0.8% to 8% are derived from cranial nerve V, and 0.5% to 1.9% develop from cranial nerve VII (Miller 1988; Macfarlane and King 1995; Strauss and Post 1995; Sarma et al 2002). Tumors of the remaining cranial nerves are extremely rare in patients without neurofibromatosis type 1 or neurofibromatosis type 2. Rarely, schwannomas can develop within the parenchyma of the brain or intrasellar region (Sharma et al 1993; Sharma et al 1998; Sarma et al 2002; Honegger et al 2005).

Vestibular schwannoma. The majority of schwannomas (85% to 90%; approximately 2000 to 3000 per year) arise from the vestibular branch of cranial nerve VIII. Rarely, tumors can develop from the cochlear branch. Because the Schwann cell-glial junction is variable, the tumor location may vary and can range from a lateral position near the inner ear or inside the labyrinth, to a medial position at the porus acusticus, to completely within the cerebellopontine angle (Miller 1988; Macfarlane and King 1995; Neff et al 2003; Skolnik et al 2016). Schwannomas can develop from either the superior or inferior division of the vestibular nerve, with an approximately equal incidence (Jackler and Pitts 1990). In general, these tumors are slow-growing and benign neoplasms that have an indolent evolution. In 75% to 80% of cases, the growth rate is estimated to be 1 mm to 2 mm per year (Wazen et al 1985; Thomsen and Tos 1990; Bederson et al 1991; Nedzelski et al 1992). The rate of growth may be slower in older patients (Rosenberg 2000). The growth of a vestibular schwannoma can be broken down into 3 stages: (1) canalicular, (2) cisternal, and (3) brainstem compressive (Miller 1988; Jackler and Pitts 1990; Selesnick and Jackler 1992). In the canalicular stage, the tumor gradually fills the internal auditory canal, expanding from a lateral position near the inner ear toward the porus acusticus. Adjacent nerves (VII and VIII) are compressed against the walls of the internal auditory canal and are often thinned out. Osseous erosion of the internal auditory canal is common, especially the posterior lip of the porus acusticus. With further growth, the tumor emerges from the porus acusticus into the cerebellopontine angle, and enters the cisternal stage. As the tumor expands into the cerebellopontine angle cistern, the seventh and eighth cranial nerves and the anterior inferior cerebellar artery are displaced. Typically, the seventh cranial nerve is stretched over the capsule of the tumor. The function of the facial nerve may progressively worsen as the cerebellopontine angle portion of the tumor causes stretching of the nerve over the anterior lip of the porus acusticus. Once the cerebellopontine angle cistern is filled, the tumor enters the brainstem compressive stage as contact is made with the pontomedullary junction. Progressive brainstem compression ensues as the tumor continues to enlarge. When the cerebellopontine angle portion of the tumor reaches 3 cm to 4 cm in diameter, the fourth ventricle is often shifted past the midline, and hydrocephalus may develop. During this same period, superior extension of the tumor usually causes displacement of the trigeminal nerve.

The most common symptoms of vestibular schwannomas are unilateral sensorineural hearing loss (96%), unsteadiness (77%), tinnitus (71%), headache (29%), mastoid pain or otalgia (28%), facial numbness, diplopia, and vertigo (Bentivoglio et al 1988; Miller 1988; Jackler and Pitts 1990; Selesnick and Jackler 1992; Macfarlane and King 1995; Matthies and Samii 1997a). In most patients, the initial symptom is unilateral sensorineural hearing loss; it may have been present from 1 to 5 years (mean 3.7 years) (Matthies and Samii 1997a). The loss is gradually progressive in 80% to 90% of cases, and sudden in 10% to 20% of cases (possibly caused by occlusion of the internal auditory artery). Sensorineural hearing loss develops from a combination of tumor-induced interference with cochlear vascular supply and compression of the cochlear nerve within the internal auditory canal. Mild unsteadiness is usually not the initial complaint, but has been present for several years in most patients. Tinnitus is usually unilateral, confined to the affected ear, low grade in intensity, and constant. Headache, mastoid pain, and otalgia are often present in patients with large tumors that impinge on local dural and osseous structures, or that have caused elevated intracranial pressure. Although rare, patients can present with an acute severe headache associated with nausea and emesis from schwannomas that have hemorrhaged (Kim et al 1998). Facial numbness is usually confined to the lower face; facial weakness is uncommon. Symptomatic paroxysmal vertigo is infrequent and is usually not accompanied by nausea.

On neurologic examination of patients with vestibular schwannoma, the most common finding is unilateral

sensorineural hearing loss (Miller 1988; Jackler and Pitts 1990; Selesnick and Jackler 1992; Macfarlane and King 1995; Matthies and Samii 1997a). Approximately 90% to 95% of patients have abnormalities of hearing. Preservation of hearing is possible only if the tumor is small (less than 1.5 cm) or confined to the cerebellopontine angle cistern. In 50% of patients at presentation, hearing loss is the only neurologic sign. Although the symptom of unsteadiness is common, most patients have normal or mildly affected gait and station. In many of these patients, unsteadiness is related to dizziness and other signs of vestibular dysfunction (Matthies and Samii 1997a). Large tumors may cause frank ataxia or dysmetria from brainstem or cerebellar compression, but these signs are infrequent. In 7% to 15% of patients, particularly those with tumors larger than 4 cm in diameter, papilledema is present (Miller 1988; Macfarlane and King 1995). Horizontal nystagmus is often noted in patients with tumors greater than 2 cm in diameter (Miller 1988; Macfarlane and King 1995). Trigeminal dysfunction, typically in the form of a diminished corneal reflex or partial facial hypesthesia, is noted in more than half the patients; hemifacial anesthesia is rare (Selesnick and Jackler 1992). Diminished corneal sensation is present in 30% of medium-sized and 60% of large-sized vestibular tumors. Paresis of the lower cranial nerves (IX, X, XI, XII) is uncommon and appears as a late sign in large tumors that grow in a medial and inferior direction toward the jugular foramen (Hanabusa et al 2001). Long tract signs (eg, hemiparesis, spasticity, hyperactive reflexes) from severe brainstem compression are rare in modern series (Selesnick and Jackler 1992).

Trigeminal schwannoma. Trigeminal schwannomas can arise from any portion of the fifth cranial nerve (sensory or motor root, gasserian ganglion, 1 of 3 major divisions, or peripheral branches); however, the most common origin is ganglionic (McCormick et al 1988; Miller 1988; Pollack et al 1989; Strauss and Post 1995; Krishnamurthy et al 1998; Sarma et al 2002; Zhang et al 2009; Skolnik et al 2016). These tumors can be categorized by origin of location; middle cranial fossa (50%), posterior fossa (30%), or dumbbell shaped with extension into middle and posterior fossae (20%). In general, the most common symptoms are referable to ipsilateral trigeminal nerve dysfunction (noted in 50% to 60% of patients) that has been present for months to years. Complaints initially consist of numbness in 1 or more of the trigeminal distributions (25% to 30%). Less often, the symptom is pain (20% to 25%), paresthesia (5% to 10%), or a combination of all 3 complaints. Although all 3 divisions can be involved, hemifacial anesthesia is distinctly rare. When pain occurs, it is usually constant and slowly progressive. The pain may sometimes resemble trigeminal neuralgia, although the paroxysms of pain are usually not associated with trigger zones and may last for hours, instead of seconds to minutes (McCormick et al 1988; Strauss and Post 1995). In patients presenting with facial pain, more than half have ganglionic tumors, and one third arise from the nerve root. Headache or diplopia is the initial symptom in 15% to 18% or 10% of patients, respectively. Loss of hearing, tinnitus, or visual disturbance is the initial complaint in less than 10% of patients. Rare or unusual symptoms include vertigo, seizure, gait difficulty, exophthalmos, and hemifacial spasm.

On neurologic examination at presentation, patients with trigeminal schwannoma typically have dysfunction of cranial nerve V (McCormick et al 1988; Strauss and Post 1995). Diminished sensation is evident along 1 or more of the trigeminal dermatomes in 80% to 90% of patients. In most of these cases, the corneal reflex will be weak or absent. Mild weakness of the muscles of mastication is found in 30% to 45% of patients. Abnormal function of other cranial nerves is noted in 75% of patients. The cranial nerves most commonly affected are VI (35%), VIII (32%), VII (23%), III (14%), II (10%), IX and X (8%), and IV (7%) (McCormick et al 1988; Strauss and Post 1995). Palsy of cranial nerve III occurs more often in middle fossa schwannomas; it is present at diagnosis in 50% of patients (Pollack et al 1989). Abnormalities of cranial nerves VIII, IX, X, and XI occur more frequently (30% to 50%) in posterior fossa schwannomas. Long tract signs (eg, hemiparesis, spasticity, hyperactive reflexes) are evident in 16% of trigeminal tumors. Although these signs can occur with middle fossa schwannomas, they are more common with posterior fossa tumors that compress the brainstem (Pollack et al 1989). Cerebellar dysfunction (ie, ataxia, dysmetria, dysarthria, nystagmus) is found in 23% of patients, and can result from compression of the cerebellum or brainstem. Exophthalmus and papilledema are present in 17% and 11% of patients, respectively. Facial-trigeminal synkinesis has been reported in a patient after recovery from surgery for a trigeminal schwannoma (Rubin et al 1999). During regeneration of the injured facial nerve, the masseter and pterygoid muscles were reinnervated, resulting in continuous deviation of the patients jaw.

Schwannomas of other cranial nerves. The majority (58%) of schwannomas of cranial nerve VII arise from the vertical segment of the nerve within the temporal bone (Miller 1988; Rocchi et al 1991; Kim et al 2003; Skolnik et al 2016). Less often, the tumors occur near the tympanic membrane or cerebellopontine angle. In most patients (50% to 90%), the initial complaints consist of facial weakness and hearing loss. Other symptoms include tinnitus (60%), vertigo (34%), otalgia, facial pain, headache, and gait ataxia (Miller 1988; Rocchi et al 1991; Strauss and Post 1995; Chung et al 1998). The symptoms are slowly progressive (mean 6 to 7 years) in 80% of patients (Rocchi et al 1991). In the other

20%, the symptoms may have an acute onset, similar to Bell palsy, or may fluctuate. Neurologic signs usually consist of peripheral facial weakness and hearing loss; less common findings include facial sensory loss, diminished or absent corneal reflex, ataxia, nystagmus, loss of taste, and dry eyes.

Schwannomas of the cranial nerves that exit via the jugular foramen (IX, X, XI) may present with the classic jugular foramen syndrome: dysphagia, weakness and atrophy of sternocleidomastoid and trapezius muscles, hoarseness, and diminished taste (Miller 1988; Sweasey et al 1991; Strauss and Post 1995; Wilson et al 2005; Bulsara et al 2008). This usually occurs with tumors that are confined to the jugular foramen. Tumors with a significant posterior fossa component (eg, most glossopharyngeal schwannomas) present differently, mimicking vestibular tumors, with symptoms of sensorineural hearing loss, tinnitus, facial weakness and numbness, and ataxia (Strauss and Post 1995; Rapana et al 1997; Vorasubin et al 2009). On neurologic examination, the findings are variable but may include hearing loss, facial weakness and numbness, nystagmus, ataxia, papilledema, palatal weakness, reduced gag reflex, ipsilateral vocal cord paralysis, and weakness of the sternocleidomastoid and trapezius muscles. A review of the literature over the past 100 years found 42 cases of glossopharyngeal schwannoma (Vorasubin et al 2009). In 84% of the cases, patients presented with vestibulocochlear symptoms, along with midfrequency sensorineural hearing loss, which is different from the high-frequency pattern usually present in vestibular schwannomas.

Schwannomas of the ocular motor nerves (III, IV, VI) are extremely rare; tumors of cranial nerve III are the most common of this group (Miller 1988; Mehta et al 1990; Tung et al 1991; Jackowski et al 1994; Strauss and Post 1995; Santoreneos et al 1997; Mariniello et al 1999; Iijima et al 2014; Kauser et al 2014; Inoue et al 2015). Ocular motor schwannomas arise most often in the interpeduncular cistern and less often in the cavernous sinus or orbit. The duration of symptoms before diagnosis is typically shorter for this group of tumors than for other schwannomas, averaging 9 to 13 months (Mehta et al 1990; Tung et al 1991; Jackowski et al 1994; Santoreneos et al 1997). The presenting complaints are usually diplopia and headache. Other symptoms may include visual loss (compression of cranial nerve 2), facial sensory loss, weakness, gait disturbance, sensory loss, ataxia, and proptosis. Neurologic signs most commonly reflect palsy of the parent nerve (eg, exotropia, ptosis, anisocoria) and other cranial nerves affected by tumor compression (eg, visual loss, facial sensory loss). Hemiparesis, ataxia, or dysmetria may be noted if the tumor is compressing the brainstem. Rarely, a large oculomotor nerve schwannoma can present with acute hydrocephalus and mental status changes (Iijima et al 2014).

Schwannomas of cranial nerve VII present with suboccipital or nuchal headache in 70% to 75% of cases, often associated with nausea and vomiting (Strauss and Post 1995). Due to frequent compression of nerves in the adjacent jugular foramen, other common (65% to 70%) symptoms include dysphagia, hoarseness, and weakness of sternocleidomastoid and trapezius muscles. In addition, patients may complain of weakness (60% to 65%), ataxia, vertigo, and facial numbness. The most consistent finding on neurologic examination is hemiatrophy and fasciculations of the tongue with ipsilateral deviation during protrusion. Other frequent signs include papilledema, ipsilateral palatal deviation, reduced gag reflex, hemiparesis and spasticity, nystagmus, ataxia, and weakness of the sternocleidomastoid and trapezius muscles.

Schwannomas of cranial nerve XII (ie, hypoglossal schwannomas) are very uncommon and present with a combination of tongue atrophy and weakness, along with vertigo, headache, and other symptoms related to compression of the cerebellum and brainstem (Tucker et al 2007). Rare schwannomas have been reported within or near the sella turcica (Maartens et al 2003). However, the origin of these tumors remains unclear. Some authors contend the tumors are derived from the lateral sellar nerve plexus of the cavernous sinus, with secondary extension into the sella; others suggest an origin from perivascular Schwann cells.

Very rarely, schwannomas can develop within the ventricles, sometimes inducing hydrocephalus and presenting with headaches (Li et al 2015).

Schwannomas of the spine. Schwannomas of the spine usually develop from the nerve roots, with a predilection for the dorsal sensory branches. The evolution of symptoms is slowly progressive, with a median duration of 60 weeks before diagnosis (Newton et al 1995; Seppala et al 1995b; Conti et al 2004). They develop most often in the lower cervical region and at the thoracolumbar junction. The most common symptom in this group of patients is pain, either radicular (72%) or localized (59%) (Seppala et al 1995b; Conti et al 2004; Safavi-Abbasi et al 2008). Other frequent complaints include lower extremity weakness (60%), incontinence (33%), focal motor weakness (30%), gait difficulty (28%), and sensory loss. The neurologic examination often demonstrates radicular loss of reflexes and sensation. Focal muscle weakness and atrophy may be present. Myelopathic findings are noted in more than 50% of patients and include

spastic paraparesis, hyperactive lower extremity reflexes, extensor plantar responses, reduction of lower extremity sensation, and a sensory level. On rare occasions, the presentation can be rapid with development of acute spinal cord symptoms. For example, several patients have now been reported with spinal schwannomas that have bled, causing spinal subarachnoid hemorrhage and a cauda equina syndrome (Cordan et al 1999; Parmar et al 2004). An uncommon form of spinal schwannoma is the intramedullary variety (Colosimo et al 2003). The source of Schwann cells is considered to be small perivascular bundles of peripheral nerves that are present within the spinal cord. The majority of intramedullary schwannomas (62%) occur in the cervical region.

Schwannomas of peripheral nerves. The most common sites of origin are the brachial plexus, the major nerve branches of the upper limb, and the major plexus and nerve branches of the lower limb (Lusk et al 1987; Ariel 1988; Miller 1988; Kim et al 2005). The tumors usually appear on the flexor aspects of the limbs, especially the elbows, knees, and wrists. The patient complains of a mass that was initially painless that has become tender. Further growth may result in paresthesias and pain. More severe neurologic deficits only develop when tumors grow in confined spaces (eg, under firm fascia or deep to the clavicle). The examination typically shows a mass that is tender to percussion and can be moved from side to side, but not in a longitudinal manner. Percussion of the mass can often induce painful paresthesias in the distribution of the nerve (similar to Tinel sign). In most cases, sensory and motor deficits in the distribution of the affected nerve are not present. Malignant schwannomas of peripheral nerves have a similar presentation; however, the symptoms often evolve more quickly due to rapid growth (Cashen et al 2004; Carli et al 2005; Anghileri et al 2006; Widemann 2009). Patients with malignant tumors may have more severe motor and sensory deficits in the distribution of the affected nerve. Malignant peripheral tumors are most common in adults but occur in patients younger than 20 years of age in 10% to 20% of cases (Carli et al 2005; Gupta and Maniker 2007). Although uncommon (4.6%), patients without neurofibromatosis type 1 or neurofibromatosis type 2 can develop multiple schwannomas of the peripheral nerves (Ogose et al 1998). In these cases, the tumors can be located superficially or in deep tissues and tend to be smaller than their counterparts in patients with neurofibromatosis type 1 or neurofibromatosis type 2 (Anghileri et al 2006).

Neurofibromas. Small cutaneous terminal nerves are the typical location for neurofibromas in patients without neurofibromatosis type 1 or neurofibromatosis type 2 (Ariel 1988; Miller 1988; Kim et al 2005). In general, neurofibromas are considered the most common tumors of peripheral nerves. Other frequent sites include the brachial plexus, major nerves and branches of the upper extremity, and major nerves of the lower extremity (Lusk et al 1987; Miller 1988). According to several reviews of brachial plexus tumors, neurofibromas account for 46% to 54% of all resected neoplasms (Lusk et al 1987; Kim et al 2005). Similar to schwannomas, neurofibromas of the peripheral nerves present with a painless mass. The mass may become tender as it enlarges, although less often than schwannomas. Deficits of sensation and motor function are more likely with neurofibromas than schwannomas, because the parent nerve is usually engulfed within the growing tumor. Although uncommon, sporadic neurofibromas can involve the cranial cavity, orbit, cranial nerves, and spine (Carterlliei and Swoboda 2000; Lee et al 2000). When they do occur, their clinical presentation and evolution are similar to that of schwannomas of the same location (Sanguinetti et al 1993; Seppala et al 1995a). Malignant neurofibromas usually occur in patients with neurofibromatosis type 1, but can rarely occur in a sporadic fashion. Their presentation is similar to regular neurofibromas, with the presence of a painful, growing mass, along with abnormalities of sensation and strength in the distribution of the affected parent nerve. Symptoms generally evolve more rapidly with these tumors. The patients often have systemic symptoms, such as weight loss and fatigue. The neurologic examination may be normal, but more typically demonstrates loss of sensation and weakness consistent with the parent nerve.

Clinical vignette

Vestibular schwannoma. Patient A.L. was a 44-year-old male with an unremarkable past medical history, who developed episodes of dizziness, tinnitus, and mild left-sided hearing loss. The symptoms presented over several months and were slowly progressive. The initial neurologic examination was unremarkable, and presented as normal. No stigmata of neurofibromatosis type 1 were present. Audiometry revealed a mild degree of hearing loss on the left side. An MRI scan demonstrated an enhancing mass 1 to 1.5 cm in diameter in the left cerebellopontine angle, with a tail that entered the internal auditory canal. The tumor was diagnosed as a vestibular schwannoma and the patient was transferred to the operating room. A suboccipital approach was used to expose the tumor. The cochlear division of cranial nerve VIII was draped over the mass; the mass was attached to the vestibular division of VIII. After the mass was dissected away from the vestibular division, the tumor was removed piecemeal, with preservation of cranial nerve VII. After surgery the patient did well, with some preservation of left-sided hearing and only mild left facial weakness.

The facial weakness improved after several months. Follow-up MRI scans have remained free of recurrent tumor.

Trigeminal schwannoma. Patient L.D. was a 39-year-old male with an unremarkable past medical history, who initially noted severe, brief, electric shock-like pains on the right side of his face. The pain would last for 5 seconds to 10 seconds and then fade away quickly. An evaluation in a local emergency room demonstrated numbness on the right side of the face affecting the V2-3 distribution. Although the patient complained of numbness and paraesthesias of the tongue and buccal mucosa, sensation was normal. After an evaluation to rule out a stroke, the patient was given an MRI scan of the brain. The MRI showed an enhancing mass in the right Meckel cave region, consistent with a trigeminal schwannoma or meningioma. The patient was placed on carbamazepine 200 mg twice per day, with improvement of the neuralgic pain. The lesion was removed using a right temporal craniotomy and an approach that included drilling through the lateral sphenoid wing. The trigeminal ganglion had to be sacrificed to completely remove the tumor, a schwannoma. The patient developed a postoperative dysesthetic pain syndrome after surgery. Follow-up scans have remained free of residual or recurrent tumor. The pain syndrome has responded well to carbamazepine and amitriptyline. Recently, the patient has returned to full-time employment.

Biological basis

Etiology and pathogenesis

The cells of origin of sporadic schwannomas are transformed Schwann cells from cranial nerves, peripheral nerves, or nerve roots. The cells of origin of sporadic neurofibromas are a mixture of transformed Schwann cells, fibroblasts, and perineurial cells, although this remains controversial (Parisi and Mena 1993). Although the initial genesis of cellular neoplastic transformation is unknown in most cases (Rubinstein et al 1989; Salvati et al 1992), various contributory cytogenetic, chromosomal, and molecular biological events are discussed in this review. There is an association between acoustic schwannomas and prior radiation exposure, which has been corroborated by Schneider and colleagues. In a cohort of 3112 patients who had undergone irradiation as children (mean dose to posterior fossa 4.6 Gy), 43 (1.38%) developed an acoustic schwannoma, with a mean latency of 38.3 years. The relative risk was 1.14 per Gy of exposure (Schneider et al 2008). In a review of 90 patients with vestibular schwannoma and 86 controls, Muscat and colleagues studied the relative risk of cellular telephone usage (Muscat et al 2002). The relative risk was 0.9 ($p = 0.07$) and did not vary significantly based on the frequency, duration, or lifetime hours of use. A review of cell phone use and incidence of vestibular schwannoma suggested a trend toward a higher incidence, but it did not reach a significant level (Hardell et al 2003). A follow-up study by Hardell and colleagues evaluating acoustic schwannoma patients noted an increased odds ratio for tumor development in those with a greater than 15-year latency period (Hardell et al 2005). However, these data were based on a cohort of only 84 patients and need further validation. In a larger study of 678 patients with acoustic schwannoma and 3553 controls, Schoemaker and colleagues noted an overall odds ratio of 0.9 (Schoemaker et al 2005). For patients with cumulative cell phone usage of 10 years or more, there was an increase in the odds ratio to 1.8. Further long-term epidemiological studies are needed to evaluate the use of cell phones (Welling et al 2007). A meta-analysis of published data on the use of cell phones and brain tumor risk shows an increased odds ratio (2.4) for the risk of ipsilateral acoustic schwannomas for those with a latency of use of greater than or equal to 10 years (Hardell et al 2008). The odds ratio was only 1.2 for development on the contralateral side. A large study from Sweden evaluated the relative risk of occupational exposure to 50 Hz magnetic fields and the development of acoustic schwannomas (Forssen et al 2006). They reviewed the records of 793 cases and 101,762 random controls for time-weighted average, peak values, and rate of change of magnetic field exposure. The results did not support an association between low-frequency magnetic field exposure and an increased risk of acoustic schwannoma.

Three meta-analyses have been published addressing the issue of cell phone and cordless phone use and the risk of a brain tumor (Hardell and Carlberg 2009; Han et al 2009; Khurana et al 2009). In the studies by Khurana and colleagues and Hardell and Carlberg, the overall risk for brain tumors was analyzed, whereas the focus was on acoustic schwannomas in the study by Han and colleagues. Hardell and Carlberg and Khurana and colleagues analyzed all of the published studies using long-term epidemiological data, with a minimum usage of 10 years (Hardell and Carlberg 2009; Khurana et al 2009). The data suggest that using a cell phone or cordless phone for greater than 10 years approximately doubles the risk for being diagnosed with an ipsilateral brain tumor (overall estimate odds ratio 1.6 to 1.9). The increased risk applies to astrocytomas and acoustic schwannomas, but not to meningiomas. The conclusions were similar in the study by Han and colleagues, which noted an increased odds ratio of 2.4 for developing an ipsilateral acoustic schwannoma in patients using cell phones for at least 10 years (Han et al 2009).

An epidemiological study from Sweden reviewed the records of 793 patients with vestibular schwannomas and correlated them with occupational and potential occupational exposures (Prochazka et al 2010). They noted an increased odds ratio for exposure to mercury (OR 2.9) and benzene (OR 1.8), as well as a 3-fold increased risk for females working as tailors and dressmakers. The risk for tumor development did not appear to be related to socioeconomic status.

Three more studies have been published assessing the risk of cell phone use and the development of brain tumors. Two studies were specific to vestibular schwannoma and evaluated patient cohorts in Europe (INTERPHONE Study Group 2011; Schuz et al 2011). In the study by Schuz and colleagues, 2 Danish nationwide cohorts totaling 2.9 million subjects were evaluated for cell phone use and risk of vestibular schwannoma (Schuz et al 2011). An increased incidence for schwannoma was not detectable. Furthermore, of the tumors that did develop, they were not larger than expected or more likely to be on the right side of the head (where most subjects used their phone). In the INTERPHONE Study Group report, 1105 patients with newly diagnosed vestibular schwannomas were compared to 2145 case-matched controls and assessed for past mobile phone use (INTERPHONE Study Group 2011). The OR for a vestibular schwannoma with ever using a cell phone was 0.85, whereas the OR for more than 10 years of cell phone usage was 0.76. In addition, no trends were noted for subjects with increasing cumulative call time or number of calls. In the most recent meta-analysis on the topic, Repacholi and colleagues reviewed the published data for a link between cell phone use and the risk for developing brain cancer or other head and neck tumors (Repacholi et al 2012). The data did not show a statistically significant increase in risk (defined as $P < 0.05$) for brain cancer or head and neck tumors. In the most recent meta-analysis on the topic, Repacholi and colleagues reviewed the published data for a link between cell phone use and the risk for developing brain cancer or other head and neck tumors (Repacholi et al 2012). The data did not show a statistically significant increase in risk (defined as $P < 0.05$) for brain cancer or head and neck tumors. In a similar analysis of studies focused on in vivo oncogenicity, tumor promotion, and genotoxicity, they also concluded there was no statistically significant relationship between radiofrequency field exposure and genotoxic damage to brain cells. A meta-analysis of cell phone usage and vestibular schwannoma evaluated data from cohort studies, case-control studies, and registry studies (Mornet et al 2013). The cohort and registry studies were inconclusive and sometimes contradictory, and they often had short exposure durations. The case-control studies were also noted to have frequent contradictory results, as well as numerous methodological flaws. The conclusions were that at this time there is no clinical association between cell and cordless phone use and vestibular schwannomas.

Schwannomas and neurofibromas are classified as peripheral nerve sheath tumors (Russell and Rubinstein 1989; Parisi and Mena 1993). Schwannomas are composed of a homogeneous mass of transformed Schwann cells in a collagenous background. Neurofibromas also contain numerous transformed Schwann cells, but also include an admixture of transformed perineurial cells and fibroblasts.

Schwannomas typically arise from cranial nerves, spinal nerves and nerve roots, autonomic nerves, and peripheral nerves. The tumors always arise from the nerve at the transition zone between the central glial nerve sheath and the peripheral Schwann cell nerve sheath. Rarely, schwannomas can occur within the substance of the brain or spinal cord (Aryanpur and Long 1988; Russell and Rubinstein 1989; Sharma et al 1993; Sharma et al 1998; Singh et al 1993). There is a predilection for schwannomas to affect sensory nerves, although motor nerves can be involved as well.

On gross pathologic inspection, schwannomas appear as discrete, rounded, firm, encapsulated masses of a semitranslucent or milky white color arising from a nerve fascicle. The tumors may have variable amounts of cyst formation, yellowish areas of xanthomatous changes, and hemorrhage. During the early "intraneural" phase of growth, the tumor is fusiform in shape, similar to neurofibromas (Parisi and Mena 1993). As the tumor enlarges, the adjacent nerve fascicles are compressed and displaced eccentrically. The nerve fascicles are usually not infiltrated by, or encased within the mass, although they may be incorporated superficially into the tumor capsule. Large tumors may distort and compress other surrounding neural structures (eg, brainstem, spinal cord) without infiltration or invasion. The gross cut surface of the tumor may demonstrate regions that have a whorling appearance and will usually not contain nerve fibers deep to the capsule.

Sporadic neurofibromas (ie, occurring in patients without neurofibromatosis type 1 or neurofibromatosis type 2) typically arise from small cutaneous terminal nerves; less commonly, they develop in large peripheral nerves, spinal nerves, or spinal nerve roots (Russell and Rubinstein 1989; Parisi and Mena 1993). Intracranial neurofibromas of the cranial nerves are extremely rare in patients without neurofibromatosis type 1 or neurofibromatosis type 2. On gross pathologic examination, neurofibromas are soft, well-circumscribed, pedunculated, and unencapsulated gelatinous

masses of a whitish or opalescent color. Regions of cyst formation, xanthomatous changes, and hemorrhage are not seen as commonly as they are with schwannomas. During initial phases of growth, the tumor infiltrates the parent nerve, causing a localized, fusiform swelling. As the tumor enlarges, the parent nerve and those nerves around it may develop gross alterations of shape (eg, "bag of worms"), and can become encased within the mass. The gross cut surface of the tumor is devoid of the whorling texture noted in schwannomas, and contains more frequent nerve fibers deep to the capsule.

On microscopic histological examination, "classic" schwannomas are composed of a heterogeneous, biphasic architecture that contains 2 distinct regions: Antoni A and Antoni B (Russell and Rubinstein 1989; Parisi and Mena 1993; Macfarlane and King 1995; Strauss and Post 1995). In most tumors, the Antoni A regions predominate, and are organized into dense, compact rows or arrays of elongated, spindle-shaped cells that have hyperchromatic, rod-shaped nuclei and eosinophilic cytoplasm.{embed="pagecomponents/media_embed" entry_id="8655"}{embed="pagecomponents/media_embed" entry_id="8656"} The nuclei are often aligned into palisades that alternate with dense, anuclear zones of fibrillar eosinophilic material; these structures are called Verocay bodies.{embed="pagecomponents/media_embed" entry_id="8657"} Verocay bodies are less common in vestibular schwannomas than spine or peripheral nerve schwannomas. In some tumors, the cell bundles form whorls of various sizes. The Antoni B regions are loosely organized and composed of large, vacuolated, pleomorphic stellate cells with pyknotic or irregular nuclei.{embed="pagecomponents/media_embed" entry_id="8655"}{embed="pagecomponents/media_embed" entry_id="8658"} Areas of microcystic change, hyalinization of blood vessels, hemorrhage with perivascular hemosiderin deposition, lipid accumulation, and nuclear degenerative atypia are common. Mitoses and nuclear pleomorphism can be seen on occasion, but do not imply malignant potential. Cell cultures derived from Antoni A and B areas produce distinctive types of Schwann cells, as confirmed by electron microscopic studies. More detailed electron microscopic analysis of Antoni A regions demonstrates a lamellar pattern of numerous thin, elongated, cytoplasmic processes that are coated by a dense basal lamina and separated from each other by intercellular basement membrane material (Russell and Rubinstein 1989). The tissue in Antoni B regions is characterized by large numbers of organelles (eg, mitochondria, lysosomes, osmiophilic bodies) and vacuoles. Immunohistochemical typing of schwannomas demonstrates strong reactivity to S-100 protein, as well as Leu-7 and myelin basic protein. The S-100 protein is cytoplasmic in origin, and is often used to identify nerve sheath tumors (Parisi and Mena 1993; Macfarlane and King 1995). In contrast, meningiomas stain weakly for S-100 protein. A small proportion of schwannomas also stain for glial fibrillary acidic protein (Parisi and Mena 1993).

In addition to the "classic" microscopic appearance of these tumors, several less common forms exist, including the cellular, ancient, plexiform, melanotic, and malignant schwannoma variants (Russell and Rubinstein 1989; Parisi and Mena 1993; Macfarlane and King 1995; Strauss and Post 1995). The cellular schwannoma variant is characterized by a predominantly compact Antoni A pattern without well-formed palisades or Verocay bodies. Anaplastic features such as mitotic activity, high cellularity, and nuclear pleomorphism may occur, but are not associated with malignant potential (White et al 1990; Deruaz et al 1993; Parisi and Mena 1993; Casadei et al 1995). The ancient schwannoma variant demonstrates relative hypocellularity and extensive degenerative changes that include cyst formation, marked vessel hyalinization, calcification, hemorrhage, and nuclear atypia (Parisi and Mena 1993). Mitoses are usually not present. The plexiform schwannoma variant has typical histology except for a relative lack of the Antoni B component. These tumors grow in a characteristic plexiform or multinodular pattern and represent approximately 4.3% of all schwannomas, often affecting the head and neck region (Berg et al 2008). Melanotic schwannomas have melanin pigment that is abundantly scattered throughout the tumor (Parisi and Mena 1993). They typically arise in autonomic nerves and behave in a benign fashion. The malignant schwannoma variant usually arises de novo, not as anaplastic degeneration in a previously benign schwannoma (Russell and Rubinstein 1989). The characteristic features are high cellularity, increased mitotic activity, and the arrangement of spindle-shaped tumor cells into a "herringbone" pattern. Cellular and nuclear pleomorphism is more widespread and areas of necrosis are prominent. Positive reactivity to S-100 is retained in most tumors, confirming their origin from Schwann cells. Although rare, malignant schwannomas can derive from typical low-grade tumors, develop a more accelerated growth rate, and become locally invasive (Hanabusa et al 2001).

On microscopic histological examination, the typical cutaneous or spinal neurofibroma has interlacing bundles of fusiform Schwann cells with wavy nuclei within a matrix of collagen-rich and mucopolysaccharide-rich material (Russell and Rubinstein 1989; Parisi and Mena 1993).{embed="pagecomponents/media_embed" entry_id="8659"} Because of the infiltrative growth pattern of neurofibromas, axons of nerve fibers are easily demonstrated after silver

impregnation of tumor tissue. Features common to schwannomas such as palisading, Verocay bodies, and whorling are noted infrequently. The architecture and cellular appearance can vary, producing several subtypes: storiform perineural fibroma, pacinian neurofibroma, epithelioid neurofibroma, and pigmented neurofibroma (Russell and Rubinstein 1989; Parisi and Mena 1993). Rarely, neurofibromas can contain foci of classic schwannoma (Feany et al 1998). Ultrastructural studies demonstrate the presence of Schwann cells, perineurial cells, fibroblasts, and collagen. Immunohistochemical typing of neurofibromas shows strong reactivity for vimentin and S-100 in most tumors, with less frequent reactivity for Leu-7 (Russell and Rubinstein 1989; Parisi and Mena 1993). Studies of the vasculature of sporadic and neurofibromatosis type 1-associated neurofibromas reveal a high degree of vascularization (Arbiser et al 1998). In addition, abundant perivascular staining for vascular endothelial growth factor is common. Anaplastic degeneration of a previously benign sporadic neurofibroma into a malignant neurofibroma is rare in patients without neurofibromatosis type 1. Malignant neurofibromas have increased cellularity, nuclear and cellular pleomorphism, and frequent mitotic activity.{embed="pagecomponents/media_embed" entry_id="8660"} Foci of necrosis, as well as regions of metaplasia (eg, cartilage, osteoid), may be present.

Techniques that can measure the biological potential of schwannomas and neurofibromas include Ki-67, bromodeoxyuridine, MIB1, and proliferating cell nuclear antigen labeling studies, as well as flow cytometric analysis (Cho et al 1988; Nishizaki et al 1988; Nishizaki et al 1989; Louis et al 1991; Deruaz et al 1993; Casadei et al 1995). In general, these studies are consistent with benign neoplasms that usually have small growth fractions and limited aggressive biological potential. Labeling studies using Ki-67 and bromodeoxyuridine demonstrate indices of 0.5% to 1.5% in classic schwannomas (Nishizaki et al 1988; Nishizaki et al 1989; Louis et al 1991). Casadei and colleagues determined labeling indices for proliferating cell nuclear antigen and MIB1 in a cohort of nonrecurrent and recurrent cellular schwannomas (Casadei et al 1995). The mean proliferating cell nuclear antigen labeling index was approximately 5.6% for both nonrecurrent and recurrent lesions, whereas for MIB1 the mean labeling index was 6% in nonrecurrent tumors, and 8% in recurrent lesions. In contrast, a mean proliferating cell nuclear antigen labeling index of 19.5% was noted for a group of classic schwannomas by Louis and colleagues (Louis et al 1991). Deruaz and colleagues compared proliferating cell nuclear antigen labeling between classical and cellular schwannomas (Deruaz et al 1993). For their small sample of cellular schwannomas, the proliferating cell nuclear antigen labeling percentage was higher than that measured for classical schwannomas (44.6% vs. 8.1%); however, this was not correlated with more aggressive clinical behavior. DNA flow cytometric studies of classic schwannomas have shown that despite variability in ploidy status (ie, tumors may be diploid or contain aneuploid populations), the S-phase fraction is generally low: 1.0% to 2.0%; this is similar to labeling studies with Ki-67 and bromodeoxyuridine (Cho et al 1988; Nishizaki et al 1988; Nishizaki et al 1989). Flow cytometric studies of cellular schwannomas showed similar ploidy data; 62% of tumors were diploid and 30% to 35% were tetraploid or aneuploid (Casadei et al 1995). However, the overall mean S-phase fraction of 6% was higher than that seen in classic schwannomas. In the subset of aneuploid tumors, the mean S-phase fraction (11.4%) was even larger.

Cytogenetic and chromosomal studies of sporadic schwannomas reveal several consistent findings (Rey et al 1987; Couturier et al 1990; Lodding et al 1990; Fontaine et al 1991; Webb and Griffin 1991; Lanser 1992). Many of the karyotype analyses contain normal, diploid stem cells. The most common abnormality, as determined by loss of heterozygosity studies, is monosomy of chromosome 22, which has been noted in vestibular and spinal tumors (Seizinger et al 1986; Rey et al 1987; Fontaine et al 1991). In addition, the long arm of chromosome 22 can manifest deletions, inversions, and translocations. Cytogenetic analysis of cellular schwannomas has shown similar abnormalities of chromosome 22 (Lodding et al 1990). In addition, most of the abnormal clones detected were hypodiploid, including monosomy 15, loss of the X chromosome, and loss of the long arm of chromosome 3.

Because of the frequent loss of heterozygosity of chromosome 22 in sporadic and inherited schwannomas, and the results of linkage analysis studies that implicated the long arm of the chromosome, investigators began to search for a suspected tumor suppressor gene in this location that might be involved in Schwann cell growth control (Seizinger et al 1986; Rouleau et al 1987; Rouleau et al 1993; Trofatter et al 1993). Further studies in patients with neurofibromatosis type 2 localized the candidate neurofibromatosis type 2 gene to a 6 Mb region of the q12 band of the long arm of chromosome 22 (Rouleau et al 1993; Trofatter et al 1993; Lutchman and Rouleau 1996; Gusella et al 1999; Xiao et al 2003; Welling et al 2007). The neurofibromatosis type 2 gene has 17 exons that encode for 595 amino acids and produce a protein (called either “merlin” or “schwannomin”) that has extensive sequence homology with membrane-interactive cytoskeletal proteins (eg, ezrin, moesin, radixin) (Rouleau et al 1993; Trofatter et al 1993; Gusella et al 1999; Xiao et al 2003; Beltrami et al 2013; Pecina-Slaus 2013). Some data demonstrate that the expression of ezrin, moesin, and radixin remains intact in schwannomas, despite the absence of merlin, suggesting

that schwannoma tumorigenesis is not associated with loss of other ezrin, radixin, or moesin proteins (Stemmer-Rachamimov et al 1997). It is postulated that merlin plays a critical role in the formation of plasma membrane and cytoskeletal networks necessary to regulate cell adhesion and cellular proliferation (Huynh and Pulst 1996; Lutchman and Rouleau 1996; Xiao et al 2003; Welling et al 2007; Chang and Welling 2009). In support of this potential mechanism, schwannoma tumor cells have enhanced adhesion that depends on integrin chains alpha 6 beta 1 and alpha 6 beta 4 (Utermark et al 2003). Data suggest that the neurofibromatosis type 2 gene product, merlin, is under phosphorylative control and is active when serine 518 is hypophosphorylated (Surace et al 2004). Merlin loses its ability to inhibit cell growth and cell motility when S518 becomes hyperphosphorylated. Merlin appears to control the activity of PAK1, a Rac/CDC42-dependent serine/threonine kinase (Hirokawa el al 2004). Loss of functional merlin may activate PAK1, leading to transformation of neurofibromatosis type 2-deficient cells. Analysis of the neurofibromatosis type 2 gene often contains germline mutations in patients with neurofibromatosis type 2, and acquired, somatic mutations only within tumor tissue in patients with sporadic schwannomas. Numerous investigators have now revealed a wide spectrum of neurofibromatosis type 2 mutations in sporadic schwannomas (ie, 60% to 75% of analyzed tumors) that can cause abnormal expression of the merlin protein (Irving et al 1993; Bianchi et al 1994; Irving et al 1994; Jacoby et al 1994; Sainz et al 1994; Twist et al 1994; Jacoby et al 1996; Sainz et al 1996; Welling et al 1996; Welling 1998; Chang and Welling 2009). Alterations of the neurofibromatosis type 2 gene can include deletions (ranging from 1 bp to 79 bp), point mutations, splice site mutations, nonsense mutations, insertions, and missense mutations. The most common mutations are small deletions that result in frameshifts, leading to truncation of the C-terminal region of the protein product and abrogation of the ability to interact with cytoskeletal proteins (Bianchi et al 1994; Irving et al 1994; Jacoby et al 1994; Sainz et al 1994; Jacoby et al 1996; Sainz et al 1996; Welling et al 1996; Welling 1998; Welling et al 2007). Immunohistochemical and western blotting studies are consistent with the molecular data and reveal reduced or absent merlin expression in the majority of sporadic schwannomas (Gutmann et al 1997; Hitotsumatsu et al 1997; Stemmer-Rachamimov et al 1997; Harwalkar et al 1998). The absence of merlin expression appears to be universal in these tumors and is even noted in tumors that lack genetic evidence of complete neurofibromatosis type 2 gene inactivation (Stemmer-Rachamimov et al 1997). In addition, protein expression studies have not revealed the presence of truncated or abnormally sized merlin products, suggesting that mutant merlin proteins are unstable and may undergo rapid degradation (Harwalkar et al 1998). Epigenetic alterations of the neurofibromatosis type 2 gene may also play a role in schwannoma tumorigenesis (Gonzalez-Gomez et al 2003). In a series of 44 tumors, 18% had hypermethylation of the neurofibromatosis type 2 gene, resulting in silencing of gene expression. In addition, hypermethylation was noted in the retinoblastoma (Rb) and p16 genes in 15% of the tumors. Data by Kimura and colleagues implicate the calcium-dependent neutral cysteine protease calpain in the process of merlin proteolysis (Kimura et al 1998). In tissue cultures from explanted schwannomas, Schulze and colleagues induced viral transduction and stable expression of wild-type merlin (Schulze et al 2002). They noted reduced proliferation and G0/G1 arrest in affected cells. In addition, the rate of apoptosis was increased in transduced schwannoma cells. This is consistent with data from Utermark and colleagues, who noted an increased basal apoptotic rate in primary schwannoma cells in comparison to normal Schwann cells (Utermark et al 2005). Abnormalities of DNA repair mechanisms have also been implicated in the neurofibromatosis type 2 mutation process in sporadic schwannomas, with an increased ratio of somatic frameshift to nonsense mutations (Evans et al 2005). This effect appears to be age-related because it is more pronounced in older individuals. Analysis of epigenetic silencing of other genes has been attempted by Lassaletta and colleagues, including PTEN, Rb, MGMT, RASSF1A, von Hippel-Lindau, CASP8, and others (Lassaletta et al 2006). The results noted methylation of 12 of 16 genes, ranging from 9% to 27%, with a significant association between methylation and the CASP8 and RASSF1a genes. CASP8 was associated with patient age and tumor size, whereas RASSF1A was inversely correlated with the clinical growth index. More microarray studies by this same group have noted dysregulation of the MET pathway, as well as upregulation of the osteopontin gene (*SPP1*), which is involved in the degradation of the merlin protein (Torres-Martin et al 2013). A study from Wong and colleagues has provided a link between neurofibromatosis type 2 mutations and the angiogenic phenotype in schwannomas (Wong et al 2012). Schwannoma cells lacking merlin/neurofibromatosis type 2 were noted to have significant downregulation of semaphorin 3F (SEMA3F). When SEMA3F is reintroduced into tumor cells, there is normalization of neoplastic vasculature, reduced tumor burden, and extended survival in nude mouse models. Merlin appears to regulate expression of SEMA3F through the Rho GTPase family member, Rac1. It was suggested that therapies designed to increase expression or activity of SEMA3F might be of benefit.

It is known that 1 function of merlin is to bind to PIKE-L, with subsequent binding and inhibition of the enzyme phosphoinositol 3-kinase (PI3K). Reduced levels of merlin should result in higher activity of PI3K and its downstream pathway components. Data from Jacob and colleagues have demonstrated that in schwannoma cells, the PI3K pathway

is activated, with elevated activity of PI3K, total Akt, phospho-Akt, and m-TOR (Jacob et al 2008).

Involvement of other tumor suppressor genes has been unrevealing thus far. Irving and colleagues performed a loss of heterozygosity analysis on DNA from 41 sporadic vestibular schwannomas, looking for evidence of tumor suppressor genes on chromosomes 3p, 5q, 11p, 17p, 17q, and 22q (Irving et al 1993). No loss of heterozygosity was found, except for chromosome 22q (39% of cases). Bruder and colleagues studied 50 cases and reported a subset of tumors with deletions on chromosome 22q outside the neurofibromatosis type 2 locus that do not contain mutations within the neurofibromatosis type 2 gene (Bruder et al 1999). They conclude there may be heterogeneity in the oncogenesis of schwannomas and that additional genes on chromosome 22 may be important for tumor development. In a study of cellular schwannomas, Casadei and colleagues analyzed 51 tumors for the presence of elevated levels of p53 using immunohistochemical techniques (Casadei et al 1995). Twenty-six of 51 tumors (52%) stained for p53, although the percentage of positively staining cells was low in most of the tumors. Monoh and colleagues evaluated 21 tumors using restriction fragment length polymorphism analyses to evaluate for evidence that p53 is involved in schwannoma development (Monoh et al 1998). They were unable to detect loss of heterozygosity, deletions, or mutations, and concluded that p53 does not play a role in the oncogenesis of vestibular schwannomas. Cardillo and colleagues reported the expression of transforming growth factor-beta1 in a series of 31 vestibular schwannomas using immunohistochemical techniques (Cardillo et al 1999). Transforming growth factor-beta1 has been implicated in various processes, including extracellular matrix protein formation, angiogenesis, cell chemotaxis, and nervous system development. In 26 of 31 tumors (83.7%), transforming growth factor-beta1 was positively expressed within tumor cells with higher levels noted in Antoni A regions. The majority of tumors with positive expression were also found to stain strongly for transforming growth factor-beta1 within the vasculature. In a series of 30 sporadic vestibular schwannomas, Mawrin and colleagues evaluated the expression and presence of mutations in the PTEN gene, located on chromosome 10q23.3 (Mawrin et al 2002). PTEN expression was noted in 70% of the tumors and was more noticeable in the Antoni A regions. Mutations of PTEN were not detected using PCR and strand conformation polymorphism screening. Data from Thomas and colleagues revealed a 25% rate of loss of heterozygosity at the Rb gene locus, which can have a variable effect on Rb mRNA and protein levels (Thomas et al 2005). In this series of patients, Rb expression was usually increased 2- to 5-fold in comparison to controls. Levels of phospho-Rb were also frequently increased and may have an antiapoptotic function.

A paper analyzing the p14ARF/MDM2/p53 pathway suggests that alterations of p14ARF, p21, and p53 may play a role in the pathogenesis of sporadic vestibular schwannomas (Chen et al 2015). They used immunohistochemical and immunoblot techniques in a series of 58 sporadic vestibular schwannomas, and noted that p53 was upregulated in 90% of the tumors. p53 was found to contain mutations in 88% of the tumors. p14ARF expression was negative in 95% of the tumors, whereas MDM2 was overexpressed in all of the tumors. The reduced expression of p14ARF was related to aberrant DNA hypermethylation of the p14ARF promoter in 43% of cases analyzed. p21 expression was negative in all of the tumors.

An analysis of the expression of the ErbB-1 (EGFR) and ErbB-2 receptor tyrosine kinases has been reported (Wickremesekera et al 2007). Using immunohistochemical and western blotting techniques, it was noted that ErbB-2 had increased expression in vestibular schwannomas. However, the expression was less than that documented in glioblastoma multiforme. Expression of ErbB-1 was minimal in these tumors. The lack of ErbB-1/EGFR expression has been corroborated by other investigators (Prayson et al 2007). These data are in contrast to data from other researchers who have documented upregulation of ErbB-1/EGFR in sporadic and neurofibromatosis type 2-related vestibular schwannomas (Doherty et al 2008). In their series, ErbB-1/EGFR was upregulated in 62% of sporadic tumors. Further work by Blair and colleagues demonstrated EGFR and bFGF expression in archived vestibular schwannoma tissues (Blair et al 2011). Using invasion assays, it was determined that more invasive behavior was related to activation of EGFR and bFGF as well as downstream factors such as phospho-Akt and phospho-Erk. The platelet-derived growth factor receptor-beta (PDGFR-beta) has been shown by Ammoun and colleagues to be highly overexpressed in schwannoma cells. In addition, there appears to be activation of the Raf/Erk/Akt pathway in these tumor cells. Inhibitors of these pathways were able to inhibit schwannoma cell proliferation (Ammoun et al 2008). Micro-RNAs are small noncoding RNA molecules that regulate gene expression through post-transcriptional control of mRNA concentration. It is now known that miR-21 can regulate the PI3-K/Akt signaling pathway. Cioffi and colleagues evaluated the role of miR-21 in primary human vestibular schwannoma cultures and noted consistent overexpression of miR-21 in comparison to normal vestibular nerve tissue (Cioffi et al 2010). Elevated levels of miR-21 correlated with reduced levels of PTEN. When an anti-miR-21 was transfected into the schwannoma cultures, cell proliferation was inhibited, and the frequency of apoptosis was increased. Using high-throughput miRNA expression profiling in a series

of human vestibular schwannomas, Erkan and colleagues found evidence for involvement of miR-7 (Erkan et al 2011). In these tumors, miR-7 appeared to be functioning as a tumor suppressor gene, mainly affecting the activity of the EGFR, Pak1, and Ack1 oncogenic pathways. A report by Yi and colleagues evaluated the expression of stem cell genes (eg, Oct-4, Nanog) in vestibular schwannoma archived tissue, cell lines, and resection specimens, and how they respond to activation of PDGFR and EGFR (Yi et al 2012). Activation of both PDGFR and EGFR resulted in an increase in expression of the stem cell genes Oct-4 and Nanog, as well as an increase in tumorsphere-forming ability.

An analysis into the angiogenic mechanisms underlying schwannoma growth has focused on the expression of vascular endothelial growth factor and its receptor (VEGFR-1) (Cayé-Thomasen et al 2005). In a series of 27 patients, tumor tissue concentrations of VEGF and VEGFR-1 were analyzed using ELISA methods and correlated with clinical and neuroimaging parameters. The concentration of both vascular endothelial growth factor and VEGFR-1 correlated with tumor growth rate ($p<0.001$) but not with tumor size or symptom duration. Other authors have also noted high expression of VEGF and VEGFR-1 in schwannomas (Koutsimpelas et al 2007; Uesaka et al 2007). In both reports, high levels of VEGF expression correlated with higher tumor volumes. In addition, the report by Uesaka and colleagues noted that the expression of VEGF and VEGFR-1 were more prominent in recurrent tumors in comparison to primary tumors. Koutsimpelas and colleagues also analyzed the expression of basic-fibroblast growth factor (bFGF) and found it to be elevated in schwannomas and correlated with tumor volume and the microvessel density of tumors. Immunohistochemical staining for VEGF has also been shown to be relevant for malignant peripheral nerve sheath tumors. A higher degree of staining for VEGF was noted for these tumors in comparison to neurofibromas ($p = 0.004$) and schwannomas ($p < 0.001$). The high VEGF expression was positively correlated with poor survival in these patients ($p = 0.015$) (Wasa et al 2008). In an analysis of the VEGF/VEGFR axis in a series of 182 sporadic vestibular schwannomas, Koutsimpelas and colleagues noted expression of the VEGF and its receptors in all tumor samples (Koutsimpelas et al 2012). There were significantly higher levels of expression of VEGF in the cohort of recurrent tumors ($p = 0.038$), as well as in the subgroup of preoperatively irradiated tumors ($p = 0.02$). More recent work has confirmed that VEGF-A is aberrantly unregulated in vestibular schwannomas, along with frequent overexpression of hepatocyte growth factor (HGF) and the cMET receptor (Dilwali et al 2015). The 2 signaling pathways appear to regulate each other, as demonstrated in cell culture systems. In knockdown experiments of VEGF-A and cMET, cellular proliferation and tumor growth was inhibited in cell cultures.

Analysis of cell cycle-related genes has also been investigated by several authors. Neff and colleagues evaluated the expression of cyclins D1 and D3 in a series of 15 sporadic vestibular schwannomas (Neff et al 2006). Cyclin D1 was not expressed in any of the specimens, whereas cyclin D3 was expressed in 7 of 15 of the tumors. A similar analysis of cell cycle and apoptosis gene expression was performed in aggressive and typical vestibular schwannomas (Seol et al 2005). The p27 expression was reduced in 67% of aggressive tumors and only 20% of typical cases. In an analysis of 21 vestibular schwannomas, Lassaletta and colleagues noted conflicting results, with the presence of cyclin D1 expression in 52% of cases (Lassaletta et al 2007). Cyclin D1 positive tumors was more likely in tumors with nuclear degenerative changes ($p<0.0001$). Other genes (such as p21, Bax, Bcl-2, and Fas) had similar expression between aggressive and typical schwannomas. A more recent study evaluated overexpression of cyclin D1 and cyclin D3, as well as the Ki-67 labeling index, in a series of 180 surgically resected vestibular schwannomas (Jabbour et al 2016). Cyclin D1 was found to be overexpressed in 68% of the tumors, whereas cyclin D3 was noted to be overexpressed in 44% of the cohort. The overexpression of the cyclin proteins did not vary depending on the age of the patient. However, the Ki-67 labeling index did correlate significantly with age, and was higher in patients younger than 40 years of age, in comparison to those above 40 years of age (mean 4.52 vs. 3.27, respectively; $p = 0.01$).

The molecular basis underlying sporadic neurofibromas remains largely unexplored because virtually all tumors analyzed to date have been obtained from patients with neurofibromatosis type 1. In 1 report, a family was described with dysplastic nevus syndrome that had hereditary melanoma and neurofibroma tumors (Petronzelli et al 2001). Family members had germline splicing mutations associated with the CDKN2A locus, affecting both p16ink4 and p14arf mRNA processing. Loss of p16ink4 and p14arf function leads to increased activity of CDK4 and CDK6, more active phosphorylation of Rb, and loss of cell cycle control. A study by Koutsimpelas and colleagues reviewed the results of comparative genomic hybridization in a series of 20 cases of sporadic vestibular schwannoma (Koutsimpelas et al 2011). The most common loss was chromosome 22q, with additional losses of 9p. Genomic gains were noted on 17q, 19p, and 19q, as well as 16p and 16q. The authors suggested that these results were consistent with the role of other oncogenes and tumor suppressor genes in the genesis of vestibular schwannomas, in addition to neurofibromatosis type 2. Another study focusing on sporadic vestibular schwannomas evaluated the role of matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and tissue inhibitors of metalloproteinase-1 (TIMP-

1) (Moller et al 2010). Using immunoenzymatic assays on resected samples from 12 patients, it was noted that MMP-9, MMP-2, and TIMP-1 were expressed in all tumors. The tumor concentration of MMP-9 correlated with absolute tumor growth rates, but not with any clinical parameters. Levels of MMP-2 and TIMP-1 did not correlate with any biological or clinical parameters. In a study specific to sporadic vestibular schwannomas, Lassaletta and colleagues evaluated a cohort of 51 patients and correlated the presence of neurofibromatosis type 2 gene mutations with clinical parameters (Lassaletta et al 2013). An neurofibromatosis type 2 mutation was noted in 49% of the cohort, whereas 22q chromosomal loss of heterozygosity was present in 57%, and amplification of the gene was noted in 13.7%. One mutational hit of neurofibromatosis type 2 was present in 27% of tumors, whereas 2 mutational hits were noted in 45%. The presence of an neurofibromatosis type 2 mutation was correlated with no complaint of hearing loss at the time of diagnosis ($p = 0.023$), as well as with the feeling of aural fullness ($p = 0.029$). In addition, the inactivation of the neurofibromatosis type 2 gene was more frequent in smokers compared to those who had never smoked ($p = 0.048$).

Peripheral nerve sheath tumors have also been under investigation (Widemann 2009). Mawrin and colleagues evaluated the expression of somatostatin receptors (SST) in a series of schwannomas, neurofibromas, and malignant peripheral nerve sheath tumors (Mawrin et al 2005). The SST2A subtype was expressed often in schwannomas (89%), but not in neurofibromas (22%) or malignant nerve sheath tumors (15%). SST4 was almost exclusively expressed in malignant nerve sheath tumors (32%). Administration of an SST2A agonist was able to induce apoptosis in malignant nerve sheath tumor cells. The authors concluded that SST agonists might be useful for imaging or treatment of nerve sheath tumors. Microarray analysis of peripheral nerve sheath tumors was performed by Karube and colleagues (Karube et al 2006). Six genes were noted to be significantly upregulated in the malignant cases, including keratin 18, survivin, tenascin C, adenosine deaminase, collagen type VIa3,and collagen type VIIa1, whereas 1 gene (insulin-like growth factor binding protein 6) was downregulated. Protein immunochemistry verified the presence of increased amounts of survivin and tenascin C activity in malignant tumors.

The PI3K/Akt/mTOR signaling pathway was analyzed by Zou and colleagues in a series of 96 patients with malignant peripheral nerve sheath tumors (MPSNT) and compared to benign neurofibromas (Zou et al 2009b). The levels of p4EBP1, pS6Rp, and pAkt were all elevated in MPSNT in comparison to neurofibromas ($p < 0.05$), demonstrating an activation of these pathways. Although MPNST cells were sensitive to rapamycin (mTOR inhibitor), treatment resulted in enhanced pAkt and peIF4E expression. The use of PI-103 (dual PI3K/Akt/mTOR inhibitor) reduced cell growth and induced G1 cell cycle arrest, possibly through repression of cyclin D1. The same group evaluated 140 patients with MPSNT using tissue microarray and correlated these data with clinical parameters and survival (Zou et al 2009a). The survival rate at 10 years for patients with primary disease, recurrence, and systemic metastases was 31.6%, 25.9%, and 7.5%, respectively. Tumors greater than or equal to 10 cm at diagnosis, partial resection, and the presence of metastasis were all negative predictors of survival. Ki-67, vascular endothelial growth factor, p53, and pMEK were all overexpressed in MPNST in comparison to benign neurofibromas. On multivariate analysis, only tumor size and nuclear p53 expression were independent predictors of survival.

A study from Bassiri and colleagues evaluated the global proteome and phospho-proteome of merlin-deficient schwannomas in primary human tumor cells (Bassiri et al 2017). Several proteins were noted to be highly overexpressed in tumors compared to control cells, including PDZ and LIM domain protein 2 (PDLIM2). In addition, shRNA-mediated knockdown of PDLIM2 was able to significantly reduce schwannoma tumor cell proliferation. The authors concluded that PDLIM2 appears to be an excellent choice for targeted therapeutic options.

Epidemiology"

Schwannomas account for 6% to 8% of all primary brain tumors, with the majority occurring in adulthood (Newton 1994; Propp et al 2006; Kshettry et al 2015). The great majority of schwannomas are sporadic and unrelated to either neurofibromatosis type 1 or neurofibromatosis type 2. Over 85% to 90% of intracranial schwannomas affect the vestibular portion of cranial nerve VIII in the cerebellopontine angle (Miller 1988; Jackler and Pitts 1990; Macfarlane and King 1995). Estimates suggest an incidence of vestibular schwannomas of 0.8 to 1.09 per 100,000 population (Propp et al 2006; Kshettry et al 2015). The incidence increased to 2.93 per 100,000 in the 65 to 74 year-old age group (Kshettry et al 2015). Overall, the incidence appears to be increasing in recent decades. The second most common site for these tumors is the trigeminal nerve, which is affected by 0.8% to 8% of all intracranial schwannomas (McCormick et al 1988; Miller 1988; Samii et al 1995; Strauss and Post 1995). Tumors of the facial nerve are rare, accounting for 0.5% to 1.9% of intracranial schwannomas (Miller 1988; Rocchi et al 1991; Strauss and Post 1995). Although extremely

rare, sporadic schwannomas can develop from cranial nerves III, IV, VI, IX, X, XI, and XII (Miller 1988; Mehta et al 1990; Sweasey et al 1991; Tung et al 1991; Jackowski et al 1994; Strauss and Post 1995; Sarma et al 2002). In many clinical series spinal schwannomas and neurofibromas are combined; the exact incidence of sporadic spinal schwannomas is unclear (Halliday et al 1991). Estimates of their incidence range from 10% to 30% of all primary spinal neoplasms (Halliday et al 1991; Newton et al 1995; Seppala et al 1995b).

Sporadic neurofibromas of the intracranial cavity typically arise from cranial nerves, and are extremely rare in patients without neurofibromatosis type 1 or neurofibromatosis type 2. The vast majority of these tumors develop from spinal nerves, nerve roots, or peripheral nerves (Seppala et al 1995a). Exact incidence figures are unavailable for sporadic neurofibromas in these locations.

Prevention

No measures are known to prevent the development of a neurofibroma or schwannoma in sporadic patients or those at risk from associated disorders (eg, neurofibromatosis type 1 and neurofibromatosis type 2).

Differential diagnosis

The differential diagnosis of vestibular schwannomas consists of masses or other processes that can cause a progressive syndrome referable to the cerebellopontine angle and associated cranial nerves (Press and Hesselink 1988; Curtin and Hirsch 1992; Jackler and Pitts 1992; Lalwani 1992; Smirniotopoulos et al 1993; McKenzie 1994; Mafee 1995; Salzman et al 2001). This includes other primary cerebellopontine angle tumors, cysts, vascular malformations, aberrant normal vascular structures, and metastatic lesions. Vestibular schwannomas make up 80% to 90% of the masses found in the cerebellopontine angle (Lalwani 1992; Smirniotopoulos et al 1993; McKenzie 1994). The second most common tumors of the cerebellopontine angle are meningiomas (10% to 15% of cerebellopontine angle lesions); these have a similar clinical presentation to vestibular schwannomas. Meningiomas have several distinguishing characteristics on CT and MRI (Lalwani 1992; Smirniotopoulos et al 1993). Meningiomas typically grow as an oval or hemispheric mass rather than as a sphere, and usually have a broad dural attachment. On unenhanced CT, meningiomas demonstrate increased attenuation compared to the brain. There may be calcification and associated hyperostosis of adjacent bone. The porus acusticus is not enlarged when viewed using bone windows. Meningiomas have vigorous, homogeneous enhancement after iodinated contrast. On MRI, meningiomas and schwannomas are isointense relative to brain on T1-weighted images; however, meningiomas are more likely to remain isointense when using other pulse sequences (Smirniotopoulos et al 1993).{embed="pagecomponents/media_embed" entry_id="12354"} After administration of gadolinium, meningiomas diffusely enhance; tumor is not present within the internal auditory canal. In contradistinction to schwannomas, meningiomas are usually centered away from the porus acusticus. Even when they are located near the porus acusticus, they rarely enlarge or disturb the canal. In 60% to 72% of meningiomas, a tail of enhancement ("dural tail" sign) is visible along the dura (Smirniotopoulos et al 1993; McKenzie 1994). This finding is suggestive of a meningioma, but not pathognomonic. Occasionally, schwannomas and other masses can have a dural tail. The third most common mass of the cerebellopontine angle is the epidermoid inclusion cyst, making up 5% to 9% of all lesions (Lalwani 1992; Smirniotopoulos et al 1993). Patients often have a long history of hearing loss and tinnitus. On CT, epidermoid cysts are usually hypodense compared to brain (similar to water or cerebrospinal fluid). Calcification of the cyst rim is noted in 25% of cases. Enhancement is negligible within the cyst, but may occur along the rim. On MRI, epidermoid cysts are usually isointense to cerebrospinal fluid (ie, low signal intensity on T1 images and high signal intensity on T2 images), and may have a lamellated appearance. Similar to CT, the cyst does not enhance with gadolinium, except for the rim. Arachnoid cysts can also occur in the cerebellopontine angle. They have signal intensity and attenuation characteristics identical to cerebrospinal fluid and do not enhance with contrast. Many other lesions can arise in the cerebellopontine angle; each of these accounts for less than 1% of all cases. Tumors that may extend into, but not arise from, the cerebellopontine angle include: (1) exophytic brainstem gliomas; (2) ependymomas; (3) choroid plexus papillomas; (4) schwannomas of cranial nerves V, VII, IX, X, and XI; (5) jugular foramen paragangliomas; (6) lipomas; and (7) metastases (Lalwani 1992; Smirniotopoulos et al 1993; Salzman et al 2001; Preuss et al 2008). Metastatic tumors usually arise in the cerebellopontine angle unilaterally but can be bilateral in approximately 40% of cases (Preuss et al 2008). Melanoma is the most common type of tumor to present in this fashion. Vascular processes such as aneurysm, malformations, and aberrant loops of normal blood vessels can develop in the cerebellopontine angle. Enhancement on CT and a flow void on MRI are diagnostic of a vascular process. Rarely, infectious processes can develop in the cerebellopontine angle, such as tuberculomas and cysticercosis. Benign vestibular conditions (eg, Ménière disease) can suggest vestibular

schwannoma with symptoms and signs of hearing loss, tinnitus, nystagmus, and vertigo (Mafee 1995). However, tumor can be ruled out by a careful history (ie, fluctuating symptoms that occur in attacks, bilateral involvement in approximately 20%) and a normal enhanced MRI scan.

Trigeminal schwannomas have a similar differential diagnosis to vestibular tumors (Miller 1988; Yuh et al 1988). Approximately 30% to 35% of tumors in the Meckel cave region are trigeminal schwannomas. The remainder includes meningiomas, epidermoids, chondromas, chordomas, lipomas, and metastatic lesions. The same differential can be applied to schwannomas of the remaining cranial nerves.

The differential diagnosis of spinal schwannomas and neurofibromas consists of other tumors and numerous benign conditions that can cause myelopathy or radicular symptoms (Sanguinetti et al 1993; Newton et al 1995). Tumors to be considered in the differential include meningiomas, exophytic ependymomas and astrocytomas, epidermoid cysts, dermoids, lipomas, and teratomas. Benign conditions to be considered include syringomyelia, multiple sclerosis, transverse myelitis, spondylosis, herniated disc, and infection (eg, Lyme disease, syphilis). The majority of these diseases can be differentiated from a spinal schwannoma or neurofibroma by a careful general and neurologic examination, cerebrospinal fluid analysis, and enhanced MRI scan.

The differential diagnosis of peripheral nerve schwannomas and neurofibromas consists of other neoplasms such as malignant peripheral nerve sheath tumors, lipomas, metastases, desmoid tumors, granular cell tumors, nerve sheath myxomas, lymphangiomas, and myoblastomas (Lusk et al 1987; Ariel 1988; Miller 1988; Skovronsky and Oberholtzer 2004).

Diagnostic workup

In patients with progressive neurologic signs and symptoms suggestive of a vestibular schwannoma and cerebellopontine angle pathology, neuroimaging with MRI is the most critical diagnostic test (Jackler and Pitts 1990; Mafee et al 1990; Curtin and Hirsch 1992; Smirniotopoulos et al 1993; McKenzie 1994; Macfarlane and King 1995; Mafee 1995; Slattery et al 2003; Skolnik et al 2016). These studies should be performed with and without contrast media for the most accurate visualization of the mass, in order to assess the relationship of the mass to the internal auditory canal and other cerebellopontine angle anatomy, as well as to assist in differential diagnosis. In general, both CT and MRI have excellent sensitivity for tumors with a significant component beyond the plane of the porus acusticus and within the cerebellopontine angle cistern (Curtin and Hirsch 1992). However, MRI is consistently more sensitive than CT for small intracanalicular lesions, and is now considered the imaging modality of choice for screening patients for the presence of a vestibular schwannoma (Jackler and Pitts 1990; Curtin and Hirsch 1992; Smirniotopoulos et al 1993; McKenzie 1994; Macfarlane and King 1995; Slattery et al 2003). An MRI scan that does not show enhancement or a mass within the internal auditory canal rules out the diagnosis of a vestibular schwannoma.

On T1-weighted unenhanced MRI, vestibular schwannomas appear isointense or slightly hypointense relative to brain and are hyperintense compared to cerebrospinal fluid (Curtin and Hirsch 1992; Smirniotopoulos et al 1993; Macfarlane and King 1995). After administration of contrast, intracanalicular and small cisternal tumors enhance diffusely.{embed="pagecomponents/media_embed" entry_id="7841"} Most authors agree that the use of contrast significantly improves the detection rate for intracanalicular schwannomas (Welling et al 1990; Macfarlane and King 1995). Tumors as small as 2 to 3 mm can be clearly delineated from surrounding structures. Large cisternal tumors may have heterogeneous enhancement due to the presence of cystic regions and hemorrhage. On T2-weighted MRI, the tumor is hyperintense relative to brain, and may be isointense with cerebrospinal fluid. Some authors feel fast spin echo T2-weighted MRI is an equivalent screening method for acoustic schwannomas, compared to T1-enhanced images. However, a study by Zealley and colleagues demonstrates that fast spin echo T2-weighted imaging only has a 56% confidence rate, compared to T1-enhanced imaging (Zealley et al 2000). Small intracanalicular tumors are often difficult to visualize using only fast spin echo technique. Vestibular schwannomas are usually centered over the internal auditory canal when there is a cisternal component. Tapering of the cisternal mass toward the internal auditory canal and porus acusticus is usually present.{embed="pagecomponents/media_embed" entry_id="7841"} Intracanalicular tumors always have their longitudinal axis along the path of the internal auditory canal. The multiplanar capability of MRI enables the tumor and its surrounding anatomical structures to be visualized in much greater detail than CT. Other advantages over CT include the lack of beam-hardening artifact, the ability to identify vascular structures in close proximity to the tumor, and superior contrast resolution. However, CT is superior to MRI for evaluating the anatomy of the internal auditory canal and petrous temporal bone. Some data suggest that serial MRI scanning at the same facility and between different facilities is reliable, with a minimum detectable change in diameter

of 1.1 mm and enhancing volume of 0.15 cm2 (Slattery et al 2003).

On unenhanced CT, vestibular schwannomas appear isodense or hypodense, compared to the brain. After contrast administration, most tumors show homogeneous enhancement. Virtually all cisternal tumors and most intracanalicular tumors can be detected with enhanced CT (Curtin and Hirsch 1992; Smirniotopoulos et al 1993; Macfarlane and King 1995).{embed="pagecomponents/media_embed" entry_id="7838"} Small intracanalicular tumors may remain undetected due to partial volume averaging from surrounding dense bone. Similar to MRI, the mass is centered on the internal auditory canal and usually has a component tapering into the porus acusticus. In 70% to 90% of cases, erosion and enlargement of the internal auditory canal are evident on bone windows.{embed="pagecomponents/media_embed" entry_id="7839"} Calcification within the tumor is usually negligible.

Because the symptoms of hearing loss and vertigo are common in the general population and often not related to a vestibular schwannoma (only 5% to 10% of patients evaluated have a tumor), several nonimaging diagnostic tests have been employed to screen patients for neuroimaging. Most authors recommend a battery of pure tone audiometry, speech discrimination assessment, and auditory evoked brainstem responses (Jackler and Pitts 1990; Selesnick and Jackler 1992; Macfarlane and King 1995). Pure tone audiometry is abnormal in the majority of patients with a vestibular tumor. In 60% to 70%, high-frequency hearing loss is present. Larger tumors are more likely to cause audiometric abnormalities. Although pure tone audiometry may remain intact with up to 75% of cranial nerve fiber loss, speech processing is usually impaired (Selesnick and Jackler 1992). Speech discrimination deficits have been detected in 45% to 80% of patients with vestibular schwannomas. The most sensitive audiological screening method is the auditory evoked brainstem response (Jackler and Pitts 1990; Selesnick and Jackler 1992; Macfarlane and King 1995). The auditory evoked brainstem response is more sensitive and specific than all other nonimaging screening tests. Response latencies can be delayed with cochlear nerve stretching, even when hearing remains normal. The most consistent abnormality of the auditory evoked brainstem response is an interaural difference of greater than 0.3 msec in the latency of wave V (Jackler and Pitts 1990; Selesnick and Jackler 1992; Macfarlane and King 1995). The sensitivity of auditory evoked brainstem response for detecting a vestibular schwannoma is 93% to 98%, with a specificity of 90%. Intracanalicular and small cisternal tumors tend to cause delays in wave V, whereas large cisternal tumors often abolish wave V completely.

The CT and MRI appearance of schwannomas of other cranial nerves are similar to vestibular tumors except for their location (Lye et al 1987; Rigamonti et al 1987; Yuh et al 1988; Weber and McKenna 1994; Samii et al 1995; Strauss and Post 1995; Chung et al 1998; Zhang et al 2009; Skolnik et al 2016). Trigeminal schwannomas are seen as enhancing masses that usually arise near Meckel cave in the middle fossa, posterior fossa, or both.{embed="pagecomponents/media_embed" entry_id="8662"} On CT using bone windows, depending on the location of the tumor, erosion may be found affecting the foramen ovale or foramen spinosum, anteromedial portion of the petrous apex, lateral aspect of the sella turcica, anterior clinoid process, dorsum sellae, or superior orbital fissure. Schwannomas of the facial nerve are difficult to distinguish from vestibular tumors when they develop from the cisternal or canalicular segments of the nerve and are misdiagnosed in 36% of patients (Strauss and Post 1995). In more typical cases, the presence of an enhancing soft tissue mass within 1 or more segments of the fallopian canal is diagnostic of facial tumor (Chung et al 1998). The fallopian canal is often enlarged, which is seen best on CT with bone windows. Schwannomas of the jugular complex (cranial nerves IX, X, XI) are seen on CT and MRI as enhancing masses centered on the jugular foramen (Weber and McKenna 1994; Strauss and Post 1995; Rapana et al 1997).{embed="pagecomponents/media_embed" entry_id="7839"} Enlargement of the jugular foramen is common and best visualized on CT with bone windows. Hypoglossal schwannomas present on CT and MRI as enhancing masses ventral to the lower brainstem in the region of the hypoglossal canal (Strauss and Post 1995; Tucker et al 2007). Erosion of the hypoglossal canal is present in some cases. Ocular nerve schwannomas (cranial nerves III, IV, VI) are well visualized with CT or MRI as enhancing masses within the cisternal space ventral to the brainstem or the cavernous sinus. CT with bone windows often demonstrates erosion or scalloping of the clinoids, sella, petrous apex, and superior orbital fissure.

Schwannomas (and neurofibromas) of the spine and peripheral nerves can be visualized with either CT or MRI, but are more clearly delineated with MRI (Schroth et al 1987; Demachi et al 1990; Friedman et al 1992; Hu and Huang 1992; Sanguinetti et al 1993; Newton et al 1995; Lin and Martel 2001; Colosimo et al 2003; Gupta and Maniker 2007). The tumor presents as a round or lobulated, intradural (extradural components are common), extramedullary mass that often compresses the spinal cord. In some cases, the tumor may have a plaquelike appearance, covering several

spinal segments. An intradural location is suggested by widening of the anterior subarachnoid space at the margins of the mass. Although uncommon, some spinal schwannomas can be large and invasive, extending into the vertebral bodies and surrounding soft tissues (Sridhar et al 2001). On T1-weighted MRI the tumor is usually isointense or slightly hypointense relative to spinal cord and hyperintense relative to cerebrospinal fluid. Enhancement is often diffuse after contrast administration, but may be heterogeneous in tumors with cystic degeneration, necrosis, or hemorrhage (Schroth et al 1987; Demachi et al 1990; Friedman et al 1992). With T2-weighted images, the signal intensity is variable, depending on the relative amounts of Antoni A and B zones, cystic degeneration, and hemorrhage (Hu and Huang 1992). Most tumors have high signal intensity relative to spinal cord, similar to cerebrospinal fluid. However, tumors that contain hemorrhage or old blood products may have low signal intensity. Although uncommon, cystic schwannomas and neurofibromas have been described and delineated by MRI (Parmar et al 2001). The presence of internal septa, irregularity of walls, differences in the thickness of the walls, and hyperintensity of the cystic contents are suggestive of a nerve sheath tumor. MRI can clearly delineate schwannomas and neurofibromas of the peripheral nerves and differentiate them from surrounding normal soft tissues (Lin and Martel 2001). The rare intramedullary schwannoma can be suspected on MRI by the presence of a small to medium-sized mass that is well circumscribed, is associated with central cord edema and without syringomyelia, and demonstrates marked gadolinium enhancement (Colosimo et al 2003). Benign neurofibromas and malignant peripheral nerve sheath tumors can also be detected with the use of FDG-PET scanning (Gupta and Maniker 2007; Son et al 2007; Ferner et al 2008). Another group has shown that FDG-PET results can be predictive of future growth of plexiform neurofibromas. In a study of 18 patients, tumors with standardized uptake values greater than 2 were significantly more likely to grow in the subsequent year ($p = 0.016$) in comparison with tumors with lower standardized uptake values. The authors suggest that FDG-PET can be used to predict neurofibroma growth rates (Fisher et al 2008).

A positron emission tomography study using 2-deoxy-2-fluoro-(18)F-D-glucopyranose (18F-FDG) attempted to analyze the factors involved in glucose transport and vascular formation in a series of patients with cranial and spinal nerve schwannomas (Hamada et al 2009). The standardized uptake value correlated with tumor size (< 5 cm vs. > 5 cm; $p < 0.05$) and microvascular density (negative vs. positive; $p < 0.05$). The retention index positively correlated with the expression of vascular endothelial growth factor in the tumors (negative vs. positive; $p < 0.05$). Glucose transporter protein expression (ie, Glut-1, Glut-3) did not correlate with the standardized uptake value or the retention index.

Angiography and myelography are less useful in the era of CT and MRI, and are usually not required for small intracranial or spinal schwannomas (Jackler and Pitts 1990; Samii et al 1995; Seppala et al 1995b; Strauss and Post 1995). Angiography may be helpful preoperatively if an aneurysm or malformation is suspected in the differential diagnosis. For large tumors, angiography is often necessary to delineate regional vascular anatomy.

Management

The majority of schwannomas and neurofibromas are benign, slow-growing tumors with little or no capacity for infiltration of surrounding neural tissues. Therefore, the focus of initial management has traditionally been aggressive surgical resection (Jackler and Pitts 1990; Macfarlane and King 1995; Samii et al 1995; Seppala et al 1995a; Seppala et al 1995b; Strauss and Post 1995). This approach is appropriate for most intracranial, spinal, and peripheral nerve schwannomas and neurofibromas because complete surgical extirpation is often curative. However, in certain cases of vestibular schwannoma, it is not always clear whether to proceed directly with surgical intervention or to carefully observe the patient (Fucci et al 1999; Mirz et al 1999; Rosenberg 2000; Nutik and Babb 2001; Al Sanosi et al 2006). In the MRI era, many vestibular tumors are detected at an early stage as small, intracanalicular or cisternal lesions less than 2.0 cm in diameter. When treated conservatively, approximately 20% to 60% of these small tumors do not enlarge during the period of observation (Wazen et al 1985; Thomsen and Tos 1990; Bederson et al 1991; Nedzelski et al 1992; Macfarlane and King 1995; Fucci et al 1999; Mirz et al 1999; Rosenberg 2000; Flint et al 2005; Al Sanosi et al 2006; Ferri et al 2008; Martin et al 2008; Bakkouri et al 2009; Sughrue et al 2010). Of those tumors that do enlarge, 75% to 80% grow slowly, at a rate of 1 mm to 2 mm per year. The growth rate may be even slower in elderly patients. For example, in a series of 70 patients over 65 years of age followed by Rosenberg over a mean follow-up period of 4.8 years, only 4 patients (5.7%) required surgical intervention (Rosenberg 2000). The growth rate does not seem to correlate significantly with patient age, initial tumor size, or duration of symptoms (Bederson et al 1991; Nedzelski et al 1992; Fucci et al 1999; Mirz et al 1999; Bakkouri et al 2009). In more than 383 patients treated in an expectant, conservative manner, tumor behavior during the initial follow-up period of 12 to 58 months was predictive of further growth (Bederson et al 1991; Nedzelski et al 1992; Fucci et al 1999; Mirz et al 1999; Al Sanosi et al 2006; Ferri et al 2008). Tumors were likely to remain quiescent if they demonstrated little or no growth during the observation period.

Conversely, tumors that subsequently required surgery grew steadily during the observation period, often with an accelerated growth rate (greater than 2 mm per year). These data have led many authors to adopt a conservative, observational approach for the following patients: any patient with generally poor health, elderly patients with tumors less than 10 mm in size, elderly patients reluctant to proceed with surgery, and any patient with significant hearing loss in the opposite ear (Jackler and Pitts 1990; Bederson et al 1991; Nedzelski et al 1992; Macfarlane and King 1995; Fucci et al 1999; Mirz et al 1999; Bakkouri et al 2009). Tumors with a growth rate equal to or greater than 2 mm per year should be considered for surgical removal. In general, the delay in surgical intervention does not appear to result in more morbidity for the patient (Flint et al 2005; Ferri et al 2008). In a comparison of conservative versus primary surgical management of acoustic schwannomas, Martin and colleagues noted that facial nerve preservation ($p < 0.001$) and hearing preservation ($p < 0.000$) were both superior in the conservatively treated cohort of patients (Martin et al 2008). Conservative approaches are unjustified in most young patients, whose tumors generally have accelerated growth rates, and in patients with tumors exceeding 2.5 cm in diameter. A meta-analysis of the conservative approach literature reviewed the data on 982 patients to assess hearing outcomes (Sughrue et al 2010). Patients with lower rates of tumor growth (≤ 2.5 mm/year) had significantly higher rates of hearing preservation in comparison to those with higher growth rates (75% vs. 32%, $p < 0.0001$). The authors concluded that a rapid growth rate (ie, > 2.5 mm/year) was a better predictor of hearing loss than the initial size of the tumor in patients with tumors less than 25 mm in diameter. A natural history study with a focus on neuroimaging techniques followed 178 consecutive, untreated vestibular schwannoma patients using 3 different approaches: a mm/year model, a cm/year model, and a volume doubling time-based model (Varughese et al 2012). A mean growth rate of 4.40 years was noted for the volume doubling-based method, versus 0.66 mm/year and 0.19 cm/year with the other models. The volume doubling-based technique was felt to be the most clinically relevant growth model and the most accurate.

Surgical resection of vestibular schwannoma. Surgical resection is the treatment of choice for most patients with a vestibular schwannoma. Complete removal is usually attempted in all patients, except for selected cases (eg, elderly patients) wherein a shortened procedure may significantly reduce potential morbidity and mortality. Three surgical approaches are used for vestibular schwannoma removal: (1) suboccipital (retrosigmoid), (2) translabyrinthine (anterosigmoid), and (3) middle fossa (subtemporal) (King and Morrison 1980; Bentivoglio et al 1988; Jackler and Pitts 1990; Jackler and Pitts 1992; Macfarlane and King 1995). Each has specific advantages to offer, based on selection criteria that include tumor size, depth of internal auditory canal penetration by tumor, hearing status, exposure of the facial nerve, and patient age (Jackler and Pitts 1992). In general, the ability to perform a complete resection and preserve cranial nerve function correlates strongly with tumor size and is most favorable in tumors less than 1 cm in diameter.

The suboccipital or retrosigmoid approach uses a craniectomy just posterior to the sigmoid sinus; exposure of the tumor and cerebellopontine angle is excellent (Bentivoglio et al 1988; Jackler and Pitts 1990; Jackler and Pitts 1992; Samii and Matthies 1997a; Ojemann 2001).{embed="pagecomponents/media_embed" entry_id="8663"} The major advantages of this approach are the level of exposure and the possibility of preserving hearing. Disadvantages include the need for cerebellar retraction (with an associated increased incidence of postoperative dysmetria) and frequent postoperative headaches. Many surgeons use this approach for tumors less than 2 cm in patients with good hearing, and for large tumors that extend toward the jugular foramen (Jackler and Pitts 1990; Jackler and Pitts 1992; Macfarlane and King 1995; Samii and Matthies 1997a; Ojemann 2001). A retrosigmoid transmeatal approach is particularly good for “extra-large” tumors (greater than 4 cm in diameter) that require extensive exposure for tumor resection and preservation of cranial nerve function (Jung et al 2000).

The translabyrinthine or retrosigmoid approach uses a craniotomy of the lateral portion of the temporal bone, including the mastoid air cells and semicircular canals, to gain exposure of the internal auditory canal and cerebellopontine angle (King and Morrison 1980; Jackler and Pitts 1992; Lanman et al 1999; Sluyter et al 2001). The advantages of this approach are that minimal cerebellar retraction is necessary, cerebellopontine angle exposure is good, all drilling of the temporal bone is completed before the dura is opened, the entire intratemporal course of the facial nerve is accessible, and the incidence of postoperative headache and cerebrospinal fluid leakage is reduced. The major disadvantages of the translabyrinthine approach are that hearing is irrevocably abolished and exposure may be limited inferiorly by the jugular foramen (Jackler and Pitts 1990; Jackler and Pitts 1992; Macfarlane and King 1995). Most surgeons recommend this approach for all intracanalicular and medium-sized cisternal tumors associated with poor hearing, selected tumors with deep internal auditory canal penetration associated with good hearing, and most large cisternal tumors exceeding 3 cm (Jackler and Pitts 1992; Lanman et al 1999; Sluyter et al 2001).

The middle fossa, or subtemporal approach, uses a small temporal craniotomy anterosuperior to the external auditory canal. The facial nerve is usually draped over the top surface of the tumor with this exposure, and must be manipulated for tumor removal. The middle fossa approach is most often used for intracanalicular tumors or small cisternal tumors (less than 5 mm beyond the porus acusticus); exposure of the cerebellopontine angle is minimal. The advantages of this approach are the possibility of sparing hearing and the low incidence of postoperative headaches as much of the procedure is extradural (Jackler and Pitts 1990; Jackler and Pitts 1992; Irving et al 1998; Brackmann et al 2000; Gonzalez et al 2000). In a direct comparison of hearing preservation after use of the retrosigmoid or middle fossa approaches, the middle fossa method demonstrated significantly improved results (52% vs. 14% of patients with Class B or better hearing; $p = 0.009$) (Irving et al 1998). The middle fossa approach is more likely to achieve hearing preservation (1) when the patient has adequate preoperative hearing, (2) if the auditory evoked brainstem response shows shorter latency value, and (3) when the tumor arises from the superior vestibular branch of the nerve (Brackmann et al 2000). Disadvantages of the middle fossa approach include restricted cerebellopontine angle exposure, increased potential for facial nerve trauma, and complications from retraction of the temporal lobe (ie, epilepsy, dysphasia, cerebral hematoma).

Reports by several authors document the potential benefits of using endoscopy during surgical resection of vestibular schwannomas (Goksu et al 1999; Wackym et al 1999). The major benefits are higher magnification (to better define neurovascular anatomy of the posterior fossa), improved visualization of the tumor (especially within the internal auditory canal), and a reduced risk of postoperative cerebrospinal fluid leakage.

Intraoperative cranial nerve monitoring has emerged as an excellent method for potentially reducing the morbidity of vestibular schwannoma resection (Jackler and Pitts 1990; Harper et al 1992; Yingling and Gardi 1992; Glasscock et al 1993; Macfarlane and King 1995). This technique assists in identifying cranial nerves in the operative field (using intracranial electrical stimulation), and facilitates their dissection from tumor while minimizing significant trauma. Commonly monitored motor nerves include the facial, trigeminal, and spinal accessory. Postoperative function of cranial nerves V, VII, and XI is significantly improved when monitoring is used for tumor resection (Wiet et al 1992; Yingling and Gardi 1992; Strauss 2002). This is especially important for large medially placed tumors; in 36% of patients in 1 series, the facial nerve was split in its passage through and around the mass (Strauss 2002). The auditory nerve is monitored using auditory evoked brainstem response only during hearing preservation operations (Ojemann et al 1984; Harper et al 1992; Glasscock et al 1993; Matthies and Samii 1997b). The benefits of operative monitoring of cranial nerve 8 are controversial, but procedural morbidity is probably reduced in some patients with tumors less than 2 cm (Jackler and Pitts 1990; Harper et al 1992; Yingling and Gardi 1992; Matthies and Samii 1997b). Furthermore, some authors contend that the quality of the preoperative auditory brainstem response positively correlates with postoperative cranial nerve VIII function and extent of hearing preservation (Matthies and Samii 1997c).

Overall, the mortality of vestibular schwannoma removal is 1% to 2% for an experienced surgeon (Mahboubi et al 2014). Most of the fatalities occur in elderly patients or patients with large tumors. Almost 50% of these deaths are caused by medical complications such as pulmonary embolism, myocardial infarction, and pneumonia. Potential complications are numerous and include vascular injury, hemorrhage (0.5% to 2%), cerebellar injury (1% to 2%), cranial nerve injury, headache (10% to 30% last 4 weeks or more), vertigo, pneumocephalus, meningitis (2% to 6%), aseptic meningitis (5% to 10%), cerebrospinal fluid leakage (10% to 30%), hydrocephalus, and various medical conditions (King and Morrison 1980; Bentivoglio et al 1988; Jackler and Pitts 1990; Jackler and Pitts 1992; Wiet et al 1992; Macfarlane and King 1995; Samii and Matthies 1997a; Samii and Matthies 1997b; Pirouzmand et al 2001; Mahboubi et al 2014). There is no difference in the rate of postoperative cerebrospinal fluid leak between the rectosigmoid and translabyrinthine approaches (Brennan et al 2001). However, leaks from translabyrinthine approaches more often need surgical repair.

After resection of a vestibular schwannoma, follow-up imaging with MRI is recommended. One study suggests that for uncomplicated cases with a complete resection, initial follow-up imaging should be at 1 year (Bennett et al 2008). Patients with residual enhancement and/or subtotal resections, or underlying neurofibromatosis type 2, should undergo follow-up MRI on a more frequent and consistent basis.

Surgical resection of other cranial nerve, spinal, and peripheral nerve schwannomas. The basic principles of surgery for schwannomas from other sites are similar to those for vestibular tumors. In most cases, a complete resection is curative; subtotal removal often results in eventual recurrence of tumor. The most common operation for resection of a trigeminal schwannoma uses a subtemporal-intradural approach (McCormick et al 1988; Miller 1988;

Pollack et al 1989; Samii et al 1995; Strauss and Post 1995; Sarma et al 2002; Moffat et al 2006; Zhang et al 2009). This technique is best for tumors in the middle fossa, Meckel cave region. Tumors that have significant extension toward the cavernous sinus and superior orbital fissure may require a frontotemporal-transsylvian approach.{embed="pagecomponents/media_embed" entry_id="8662"} For tumors that are small and confined mainly to the Meckel cave region, some authors suggest a transpterygoid, endoscopic approach, which is fairly noninvasive, yet still provides enough exposure for a complete resection (Raza et al 2014). Tumors confined mainly to the posterior fossa are resected using a suboccipital approach in most cases, although some authors prefer the orbitozygomatic extradural or the subtemporal-infratemporal approaches instead, depending on the branch of the nerve involved (Krishnamurthy et al 1998). A combined approach is necessary for dumbbell-shaped tumors; for instance, the extradural zygomatic middle fossa approach. With this technique, Al-Mefty and coworkers were able to perform gross total resections with excellent preservation of cranial nerve function (Al-Mefty et al 2002). Intraoperative monitoring may be helpful in some cases (Strauss and Post 1995). Using conventional techniques, the mortality rate is 2% to 3%, with total or near-total removal of tumor in 70% to 75% of cases (Samii et al 1995; Strauss and Post 1995; Zhang et al 2009). However, the recurrence rate approaches 50% in many series. Some authors recommend more extensive skull base approaches for resection, claiming that improved tumor exposure and ease of dissection allow for more frequent complete and improved clinical outcome (Taha et al 1995; Yoshida and Kawase 1999; Moffat et al 2006; Fukaya et al 2010). For example, Fukaya and colleagues reported the surgical results of a series of 57 trigeminal schwannomas, most of which underwent resection using a skull base approach (Fukaya et al 2010). Complete resection was accomplished in 42 of 45 patients (90%), with no surgery-related mortalities. The most common surgical complications of skull base surgery are cranial nerve injury, cerebrospinal fluid leak, meningitis, and hydrocephalus. Facial nerve schwannomas are resected using an approach based on the extent and location of the tumor: middle fossa, suboccipital, or translabyrinthine (Rocchi et al 1991; Strauss and Post 1995; Sarma et al 2002; Kim et al 2003). If hearing is poor, the translabyrinthine approach is recommended. If a hearing preservation operation is attempted, the preferred approach is either suboccipital or middle fossa. Complications are similar to those of trigeminal tumors. Schwannomas of the jugular complex (IX, X, XI) are resected most often using a suboccipital approach, occasionally in combination with a mastoidectomy (Sweasey et al 1991; Strauss and Post 1995; Rapana et al 1997; Wilson et al 2005; Bulsara et al 2008). Schwannomas of the ocular motor cranial nerves (III, IV, VI) are generally resected using frontotemporal or subtemporal approaches (Miller 1988; Mehta et al 1990; Tung et al 1991; Jackowski et al 1994; Strauss and Post 1995; Mariniello et al 1999; Sarma et al 2002). Tumors located mainly within the posterior fossa can be removed with a suboccipital technique. The complete resection rate for ocular motor nerve schwannomas is approximately 50% (Strauss and Post 1995). In selected cases, preservation of oculomotor nerve function can be attempted by sural nerve grafting (Mariniello et al 1999). Hypoglossal schwannomas are most often resected using a lateral suboccipital approach (Miller 1988; Strauss and Post 1995; Tucker et al 2007). The operative mortality in these patients is relatively high (6% to 7%), usually because of respiratory complications such as aspiration and pneumonia. Surgical resection of intrasellar schwannomas can be accomplished using a trans-sphenoidal approach (Honegger et al 2005). A gross total resection is often possible.

Surgical treatment of spinal schwannomas and neurofibromas is similar to that for tumors of the cranial nerves; complete resection is curative in most cases. The operative approach is usually a midline partial or total laminectomy (Seppala et al 1995a; Seppala et al 1995b; Conti et al 2004). The tumors are always attached to at least 1 nerve root. Schwannomas can be completely resected in 85% to 90% of cases without sacrifice of the parent nerve root (Seppala et al 1995b; Conti et al 2004; Safavi-Abbasi et al 2008). Radical resection is also possible for large, invasive tumors that extend into surrounding bones and soft tissues (Sridhar et al 2001). For tumors of the thoracic spine, some authors recommend resection via thoracoscopy (Dickman and Apfelbaum 1998). This technique is an excellent alternative to thoracotomy because of the smaller incision used, better cosmetic results, reduced postoperative pain, and earlier return to activity. Neurofibromas can be completely resected in 90% of cases (Seppala et al 1995a). However, in 80% to 90% of these patients the parent nerve root must be sacrificed during tumor removal. Complications most often consist of hemorrhage, wound infection, deep venous thrombosis, wound dehiscence, and pulmonary compromise (eg, embolism, pneumonia).

Schwannomas and neurofibromas of the peripheral nerves are usually solitary lesions in patients without neurofibromatosis. Surgical resection of schwannomas, when they develop from distal nerve branches, consists of simple dissection of the parent nerve from the tumor capsule and en bloc removal of the mass (Ariel 1988).{embed="pagecomponents/media_embed" entry_id="8664"} Neurofibromas are often more difficult to dissect away from the parent nerve, as it may become encased within the mass. Schwannomas of the large nerve trunks (ie, brachial or lumbosacral plexus) can also be completely resected in most cases with careful microdissection of the

parent nerve away from the tumor capsule (Lusk et al 1987). In contrast, complete resection of neurofibromas often requires sacrifice of fascicles of the parent nerve and nearby nerves that have become encased within the mass. Adherent tumor must often be dissected from remaining nerve fascicles. Some authors recommend an interfascicular approach in combination with nerve conduction testing to maximize the chance for complete resection (Kim et al 2005). With improvements in microneurosurgical techniques, some authors are recommending a "nerve sparing" approach to surgical resection of benign peripheral nerve schwannomas and neurofibromas (Russell 2007). Localized surgical approaches are not adequate for treatment of malignant schwannomas or neurofibromas (Sordillo et al 1981; Ariel 1988; Baehring et al 2003; Carli et al 2005; Gupta and Maniker 2007; Widemann 2009). These tumors generally require either radical local excision or amputation. Radical local excision involves en bloc removal of the tumor and any attached nerve, bone, muscle, and blood vessels. Normal tissue planes must be attained on all surfaces, or amputation is necessary.

Radiation therapy of vestibular schwannomas. For a small subgroup of patients with vestibular schwannomas, conventional external beam radiation therapy or stereotactic radiosurgery may be adjunctive or alternative forms of therapy (Noren et al 1983; Wallner et al 1987; Hirsch and Noren 1988; Pollack et al 1989; Linskey et al 1990; Linskey et al 1992; Flickinger et al 1991; Lunsford and Linskey 1992; Macfarlane and King 1995; Murphy and Suh 2011). Conventional radiation therapy is not indicated for patients after a complete or near-total resection. It should be considered in patients with substantial residual tumor after surgery, for recurrent tumors in advanced stages of disease, and for those patients with large tumors who are poor surgical candidates. In a review of 124 patients with vestibular tumors that received radiation therapy after subtotal tumor removal, Wallner and colleagues concluded that irradiation significantly reduced the possibility of tumor progression (Wallner et al 1987). Irradiation with doses of 5000 to 5500 cGy, administered in 180 cGy fractions, decreased the recurrence rate from 46% to 6% ($p = 0.01$). Preoperative irradiation can also be used to reduce the risk of hemorrhage during resection for patients with highly vascular schwannomas (Wallner et al 1987; Ikeda et al 1988). Doses of approximately 3000 cGy can reduce vascularity after a period of 6 to 8 weeks.

Stereotactic radiosurgery is a method of delivering focused irradiation within the boundaries of a tumor in a single fraction, using great precision (Loeffler and Alexander 1990; Battista 2009). The treatment is most often administered using a gamma knife; however, linear accelerator and proton beam units are also used and demonstrate comparable local control and complication rates (Mendenhall et al 1996; Suh et al 2000; Spiegelmann et al 2001; Friedman et al 2006). Similar to conventional external beam irradiation, radiosurgery is considered an alternative or adjunctive therapy in carefully selected patients with vestibular schwannomas (Linskey et al 1990; Linskey et al 1992; Flickinger et al 1991; Lunsford and Linskey 1992; Shetter 1997; Kondziolka et al 1998; Pollock et al 1998b; Prasad et al 2000; Suh et al 2000; Lunsford et al 2005; Likhterov et al 2007; Battista 2009; Murphy and Suh 2011; Wangerid et al 2014; Ellenbogen et al 2015). Patients most appropriate for radiosurgical therapy include those who are medically unstable, are elderly (greater than 65 years old), are contralaterally deaf, have failed an initial surgical resection, or refuse surgical intervention (Linskey et al 1992; Lunsford and Linskey 1992). Lesions less than 3 cm in diameter are most suitable for radiosurgery, although some authors feel that larger tumors (up to 4 cm) can also be successfully treated in most cases (Yang et al 2013). The most common treatment plan involves a margin dose of 16 to 18 Gy (in a single fraction) at or above the 50% isodose line, depending on the estimated tumor volume (Flickinger et al 1991; Linskey et al 1992; Lunsford and Linskey 1992; Kondziolka et al 1998). Depending on the configuration of the tumor, 1 or more isocenters are used to cover the treatment volume (average 2.5 isocenters). Clinical response as measured by CT or MRI demonstrates tumor shrinkage in 20% to 30%, stable tumor in 60% to 75%, and tumor progression in 3% to 5% (Flickinger et al 1991; Linskey et al 1992; Lunsford and Linskey 1992; Shetter 1997). More recent papers with long-term follow-up after radiosurgery have noted reduction in tumor size ranging from 62% to 81% (Kondziolka et al 1998; Prasad et al 2000; Lunsford et al 2005; Battista 2009). The estimated overall local control rate for radiosurgery is approximately 92% to 98% (Lunsford and Linskey 1992; Mendenhall et al 1996; Shetter 1997; Kondziolka et al 1998; Pollock et al 1998a; Pollock et al 1998b; Lunsford et al 2005; Friedman et al 2006; Likhterov et al 2007). A review of 208 consecutive patients, with median follow-up time of 56 months, noted growth of tumors in 30 patients (14%) (Pollock 2006). Of this cohort, only 6 had progressive tumor enlargement that required further treatment with surgical resection or radiosurgery. The conclusion of the author was that the initial enlargement after radiosurgery did not necessarily denote failure of the procedure. This has been corroborated in a study by Nagano and colleagues in which a 25% to 47% increase in tumor size was noted in over half their cohort of 100 consecutive vestibular schwannoma patients treated with radiosurgery. Peak tumor expansion was usually noted by 6 months after treatment and normalized within 12 months. High-dose treatment (ie, 3.5 Gy/min) was marginally correlated with the likelihood of tumor expansion (Nagano et al 2008). In a review of schwannomas that recurred after 1 or more attempts at surgical

resection, radiosurgery was able to achieve growth control in 73 of 78 tumors (94%) (Pollock et al 1998a). The median interval from time of treatment to objective tumor shrinkage is approximately 12 months. Loss of central tumor enhancement is observed in 75% to 80% of cases after a median interval of 6 months. This is postulated to occur by radiation-induced vascular injury, thrombosis, and occlusion. The rate of useful preservation of hearing is 50% at 6 months and 38% at 1 year (Linskey et al 1992; Lunsford and Linskey 1992; Shetter 1997). Hearing begins to decline at a median of 6 months and is not correlated with loss of tumor contrast enhancement, tumor margin dose, or tumor margin isodose. Several reviews of hearing preservation after radiosurgery for vestibular schwannoma suggest an overall rate of preservation of approximately 51% at 3 to 4 years after treatment, with doses of less than 13 Gy being more likely to maintain hearing (Kano et al 2009a; Timmer et al 2009; Yang et al 2010). The degree of hearing preservation appears to be correlated to the maximal radiation dose at the cochlea, emphasizing the need for meticulous radiation planning. Some authors have also used gamma knife radiosurgery in patients with vestibular schwannomas that have failed initial radiosurgery with a different platform (ie, LINAC) (Dewan and Noren 2008). In 8 of the tumors, shrinkage was noted on follow-up MRI. Acute complications include nausea or vomiting (21%) and headaches (10% to 12%). Although rare, hearing loss and facial weakness within 24 to 48 hours of radiosurgical treatment have also been reported (Chang et al 1998; Tago et al 2000). Delayed facial neuropathy occurs in 34% of patients with normal preoperative function and 27% of patients with abnormal preoperative function. The facial weakness improves or recovers by 6 months in most patients. Radiosurgical doses of greater than or equal to 18 Gy appear to cause permanent facial neuropathy (Miller et al 1999). Patients receiving doses of less than or equal to 16 Gy were significantly less likely to develop facial neuropathy. Longer follow-up is required before conclusions can be drawn regarding efficacy of local growth control using the reduced dose protocol. Delayed trigeminal neuropathy occurs in 32% of patients with normal preoperative function and 46% of patients with abnormal preoperative function. Trigeminal dysfunction improves, but does not resolve within 6 months in most patients. The mechanism of cranial nerve injury remains unclear, but is probably a combination of direct radiation injury, localized edema, demyelination, and vascular compromise. Although data by Linskey and colleagues suggest that the length of cranial nerve irradiated correlates with the risk of delayed injury, additional studies indicate that the dose to the brainstem may be a more important predictor of post-treatment cranial neuropathy (Linskey et al 1993; Foote et al 2001). In a review of complication rates in a cohort of 190 patients treated with a median of 13 Gy, Flickinger and colleagues noted similar local control rates to other studies using higher doses; however, there were lower rates of hearing loss, facial numbness, and facial weakness (Flickinger et al 2001). Other potential complications include worsened balance (31%), vertigo (4%), and hydrocephalus. A rare complication that has been reported more often lately is radiation-induced transformation of vestibular schwannomas. In a case report and literature review by Seferis and colleagues, they estimated that the overall risk for malignant transformation over 20 years was 25.1 per 100,000 overall, and 15.6 per 100,000 if cases of neurofibromatosis were excluded (Seferis et al 2014). In their review, the mean time to transformation was 72 months. Another radiosurgical approach is to use protons, which confer a radiobiological advantage for beam accuracy. Weber and colleagues have used proton beam radiosurgery in a series of 88 patients, with 93.6%, 5-year tumor control rates and comparatively low rates of facial and trigeminal neuropathy (Weber et al 2003). Data suggest that Gamma Knife radiosurgery results in high quality of life (median index 0.91; maximum score 1.0), along with high tumor control rates (Wangerid et al 2014). Another study compared using Gamma Knife to conservative management in a series of 237 patients with vestibular schwannomas (Breivik et al 2013). Hearing loss was similar in both groups: Gamma Knife (64%) versus conservative (76%), with a nonsignificant trend in favor of radiosurgery. There was a significant reduction in tumor volume over time in the Gamma Knife cohort. In addition, the need for further treatment was much less in the Gamma Knife cohort ($p < 0.001$).

Kruyt and coworkers used Gamma Knife to treat growing vestibular schwannomas in patients with sporadic disease and matched controls with neurofibromatosis type 2 (Kruyt et al 2017). There were 47 patients in each cohort, receiving a median margin dose of 11 Gy. The results for actuarial tumor control rates were similar in both groups -- 98%, 89%, 87%, and 87% after 1, 3, 5, and 8 years, respectively. Patients with tumor volumes less than 6 cm^3 were associated with a significantly better outcome. Hearing preservation rates and complication rates were also similar between the sporadic and neurofibromatosis type 2 groups.

A study by Bailo and colleagues evaluated the use of Gamma Knife as primary treatment in a series of 59 large acoustic schwannomas larger than 25 mm in diameter (Bailo et al 2016). Mean patient age was 63.8 years, with a median tumor volume of 5.98 cm^3 and a median marginal dose of 13 Gy. Tumor control was achieved in 98.3% of cases; 86.4% of tumors showed some volume reduction. Complications included new permanent facial nerve deficit, new or worsened trigeminal impairment, and new hydrocephalus. Larger tumor size was significantly associated with the onset of hydrocephalus. The authors concluded that Gamma Knife was safe and effective for primary treatment of

large acoustic schwannomas, especially in patients who were not good surgical candidates. A similar study from Teo and colleagues evaluated the use of hypofractionated stereotactic radiosurgery for treatment of 30 large vestibular schwannomas larger than 3.0 cm in size (Teo et al 2016). All patients were treated with 3 fractions to a median dose of 18 Gy. The 3- and 10-year Kaplan-Meier estimates of local control were 85% and 80%, respectively, with 20% requiring some form of salvage therapy. Patients that had previous surgery before radiosurgery, as well as those with neurofibromatosis type 2, had higher rates of tumor progression.

Some authors feel fractionated radiosurgery may be superior to standard radiosurgery, due to the radiobiological advantages inherent to fractionation, such as reduced risk of cranial nerve injury (Szumacher et al 2002; Sawamura et al 2003; Combs et al 2005; Likhterov et al 2007). In a series of 39 patients with vestibular schwannomas, Szumacher and colleagues noted local tumor control in 95% of the cohort at 21.8 months median follow-up (Szumacher et al 2002). At 22 months median follow-up, no new cases of cranial nerve dysfunction were noted. After fractionated radiosurgery, of those patients with functional hearing before treatment, 68% were able to maintain a similar level of function. Similar results have been reported by several groups in large cohorts of more than 100 patients (Sawamura et al 2003; Combs et al 2005). In contrast, other authors report that single-fraction linear accelerator-based radiosurgery may be as effective as fractionated methods in terms of tumor control rates (Meijer et al 2003). The Stanford group reported their experience using the Cyberknife, with minimal fractionation over 3 days (Sakamoto et al 2009). A total of 61 patients with vestibular schwannomas were treated, with a mean maximal tumor dimension of 18.5 mm. The local control rate was 98%; tumor shrinkage was noted in 29 tumors. None of the patients developed new facial weakness or trigeminal deficits. Some authors have also suggested that hypofractionated stereotactic radiotherapy can be effective (Sakanaka et al 2011). In a series of 27 patients with vestibular schwannoma, linear accelerator radiosurgery was administered to a total dose of either 30 to 39 Gy over 10 to 13 fractions, or 20 to 24 Gy over 5 to 6 fractions. Local control rates were 100% and 92% for the high- and low-dose cohorts, respectively. In addition, with this approach, minimal facial and trigeminal nerve morbidity was noted. A more recent series of patients treated with the Cyberknife has been reported by Tsai and colleagues (Tsai et al 2013). They treated 117 patients with vestibular schwannomas, and they noted a 99.1% control rate overall. Those patients with small to medium sized tumors had good hearing preservation in 81.5% of the cases.

Currently, 20% to 25% of vestibular schwannomas are treated with radiosurgery either as initial therapy or at recurrence (Pollock et al 1998b). Pollock and colleagues predict that over the next 10 years to 20 years, radiosurgery will replace surgical resection as the initial treatment of choice for these tumors (Pollock et al 1998b). Nonrandomized comparisons between series of patients treated operatively and by gamma knife suggest similar tumor growth control and a reduced risk of hearing loss, facial palsy, facial hypesthesia, and feeding problems in the radiosurgical cohort (Regis et al 2002; Karpinos et al 2003; Pollock et al 2006). In a prospective, nonrandomized comparison of stereotactic radiosurgery (N = 46) and surgical resection (N = 36), Pollock and colleagues concluded that radiosurgery was more effective in terms of facial function and hearing preservation ($p < 0.001$), as well as on several subscales of the Health Status Questionnaire (eg, physical functioning, energy/fatigue) (Pollock et al 2006). The improved results of radiosurgery were only noted for patients with small and medium sized tumors. A similar study was published out of Norway by Myrseth and colleagues in which a cohort of 91 prospective patients with small- to medium-sized vestibular schwannomas were treated with gamma knife radiosurgery (N = 63) or open microsurgery (N = 28) (Myrseth et al 2009). The results were again in favor of the radiosurgery cohort, with better preserved facial nerve function and hearing ($P < 0.001$) than the surgical group. In addition, quality of life measures were significantly better in the radiosurgery cohort.

Radiation therapy of nonvestibular schwannomas. Several authors have used radiosurgical approaches to treat nonvestibular schwannomas with excellent results, similar to the data for vestibular tumors. Pollock and colleagues treated 23 patients with tumors of the trochlear, trigeminal, jugular, and hypoglossal nerves (Pollock et al 2002). Local control rates were 96%, with a 17% rate of cranial nerve morbidity. Similar results are reported by Zhang and colleagues in a series of patients with jugular foramen schwannomas (Zhang et al 2002). Gamma knife radiosurgery has been applied to a series of 21 patients with trigeminal schwannomas (Phi et al 2007). Tumor growth control was achieved in 95% of cases. In 6 patients (27%), new or worsening cranial neuropathies were noted after treatment. In a series of 33 patients with trigeminal schwannomas, progression-free survival rates at 5 and 10 years were both 82.0% after gamma knife radiosurgery (Kano et al 2009b). In a similar study of jugular foramen schwannomas, stereotactic radiosurgery was applied to 35 tumors (Martin et al 2007). Tumors regressed in 17 patients and remained stable in 16 patients. The 5- and 10-year actuarial control rates were 97% and 94%, respectively. Preexisting cranial neuropathies improved in 20% of cases and remained stable in 77%. Data from several groups suggest that gamma knife

radiosurgery can also be of benefit for patients with facial nerve schwannomas (Litre et al 2008; Madhok et al 2009; Sheehan et al 2015). In a series of 11 patients, 10 remained stable or regressed after treatment, with satisfactory preservation of facial nerve function (Litre et al 2008). Similar results were noted from Madhok and colleagues in a series of 6 patients (Madhok et al 2009). A large multicenter study evaluated 42 patients with facial nerve schwannomas after gamma knife radiosurgery (median margin dose 12.5 Gy) (Sheehan et al 2015). Tumor control was achieved in 90% of the cohort, with actuarial tumor control of 97%, 97%, 97%, and 90% at 1, 2, 3, and 5 years, respectively, postradiosurgery. A small series of 8 patients with schwannomas of cranial nerves III, IV, and VI have been reported by Kim and colleagues (Kim et al 2008). All of the tumors had shrinkage on follow-up MRI, and several patients had improvement in diplopia.

Some authors have applied fractionated radiosurgical techniques to nonvestibular schwannomas. Zabel and coworkers used a median dose of 57.6 Gy with 1.8 Gy fractions on 13 patients (Zabel et al 2001). Local control rates were 100%, with 4 tumors decreasing in size. No new cranial nerve or brainstem deficits were noted. After maximal surgical resection, external beam radiotherapy should also be considered in selected patients with malignant peripheral nerve sheath tumors, especially those with gross residual disease (Baehring et al 2003; Carli et al 2005; Gupta and Maniker 2007; Widemann 2009). A report by Sun and associates evaluated 52 patients with trigeminal schwannomas who were treated by stereotactic radiosurgery (Sun et al 2013). The mean radiation dose was 13.9 Gy (range, 11 to 17 Gy). Neurologic symptoms or signs improved in 67%, were stable in 27%, and worsened in 4%. On MRI follow-up, there were near complete responses in 15%, partial responses in 62%, and stable disease in 10%. Tumors grew in 14%.

Chemotherapy. In general, chemotherapy has not been applied to patients with sporadic schwannomas or neurofibromas. A small phase I trial of thalidomide, an angiogenesis inhibitor, has been completed in patients with neurofibromatosis type 1 and plexiform neurofibromas (Gupta et al 2003). The drug was well tolerated up to doses of 200 mg/day. Several patients were noted to have minor responses (less than 25% reduction in size) and stabilized disease. Plotkin and colleagues tested a series of 43 patients with unresectable neurofibromatosis type 2-related and sporadic vestibular schwannomas for expression of vascular endothelial growth factor (VEGF) and VEGF receptors and attempted treatment with bevacizumab, a humanized monoclonal antibody against VEGF (Plotkin et al 2009). VEGF was expressed in 100% of the tumors, with expression of VEGFR-2 noted in 32% of all tumor vessels. Ten patients were treated with bevacizumab (5 mg/kg intravenously every 2 weeks). Tumor shrinkage was noted in 9 patients on follow-up MRI, with a median best response to treatment volume reduction of 26%. Several patients had durable responses that were maintained over 11 to 14 months. In addition, 4 of 7 evaluable patients had some improvement in hearing. A follow-up report from the same authors describes an overall cohort of 31 consecutive patients with neurofibromatosis type 2-related vestibular schwannomas treated with bevacizumab (Plotkin et al 2012). An improvement in hearing was noted in 13 of 23 evaluable patients (57%), whereas an objective response by MRI (20% or more reduction) was noted in 17 of 31 evaluable patients (55%). These results are consistent with subsequent case reports of patients treated with bevacizumab (Mautner et al 2010; Alanin et al 2015). Mautner and colleagues reported 2 patients with neurofibromatosis type 2-related vestibular schwannomas treated with bevacizumab, both of which had tumor regression of 40% or more (Mautner et al 2010). One of the patients was treated for 6 months and also had improved hearing. In the study by Alanin and colleagues, 12 patients (18 tumors) with neurofibromatosis type 2 were treated with bevacizumab (10 to 15 mg/kg) (Alanin et al 2015). Radiologic responses (ie, greater than 20% tumor shrinkage) was noted in 7 of 18 tumors (39%). Three patients had objective improvement in their hearing, and another 5 patients reported subjective neurologic improvement. Other authors have evaluated anti-VEGF therapy in an animal model (Wong et al 2010). They treated rats implanted with HE1193 or murine neurofibromatosis type 2 -/- tumors with either bevacizumab (10 mg/kg/week) or vandetanib (50 mg/kg/day). There were improvements in tumor vessel diameter, length/surface area density, and permeability in both types of tumors, with both drugs. An increase in necrosis was noted in HE1193 tumors, whereas the neurofibromatosis type 2 -/- tumors were noted to have increased apoptosis. In addition, the tumor growth rate was decreased by 50%, and the survival time was increased by 50% in both drug groups. Although chemotherapy is not generally considered to be of benefit for patients with malignant peripheral nerve sheath tumors, some authors have noted modest benefit in pediatric patients using ifosfamide-based regimens (Carli et al 2005; Gupta and Maniker 2007).

In vitro and animal model experiments with molecular chemotherapy drugs are now underway. Using an in vitro model system of schwannoma, Ammoun and colleagues have shown that sorafenib (BAY 43-9006), an inhibitor of PDGFR and c-Raf, can inhibit PDGFR-beta-mediated ERK1/2 and Akt activity and can reduce cell proliferation in schwannoma cells (Ammoun et al 2008). Another study investigated the activity of AZD6244, an inhibitor of MEK1/2 that is involved in the activation of the extracellular signal-regulated kinase pathways and cell proliferation in schwannoma cells

(Ammoun et al 2010b). At low concentrations, AZD6244 was able to abolish platelet-derived growth factor-mediated activation and cell proliferation in schwannoma cell lines. Another follow-up study by Ammoun and colleagues used receptor tyrosine kinase arrays to screen tumor samples from neurofibromatosis type 2-related and sporadic vestibular schwannomas (Ammoun et al 2010a). Eleven patient samples and 2 control samples were analyzed; all of the tumors were positive for activated epidermal growth factor receptor, and more than half were also positive for activated ErbB2 and ErbB3. Activated ERK1/2 was also noted in all of the tumor samples. Based on these results, the small molecule EGFR/ErbB2 inhibitor, lapatinib, was used to treat in vitro human schwannoma cells. Lapatinib was able to inhibit ErbB2 phosphorylation and survivin upregulation, as well as downstream ERK1/2 and Akt activation. Proliferation of schwannoma cells was inhibited. Lapatinib has also been studied in a Phase II trial by Karajannis and colleagues, in a series of 21 patients with neurofibromatosis type 2-related vestibular schwannomas (Karajannis et al 2012). Of 17 evaluable patients, 4 were noted to have an objective response by MRI, ranging from -15.7% to -23.9% reduction in enhancing volume. Four of 13 evaluable patients also had objective improvement in hearing function. Median time to overall progression (MRI or hearing) was 14 months. The estimated overall progression-free survival and volumetric progression-free survival were 64.2% and 70.6%, respectively. OSU-0312, a drug that selectively targets the Akt pathway via inhibition of PDK1, has been shown to suppress schwannoma cell proliferation and decrease phospho-Akt in culture systems (Jacob et al 2008). Follow-up studies from the same authors have noted that OSU-03012 has activity against typical and malignant schwannoma cells (Lee et al 2009). The drug was able to inhibit cell proliferation in culture, with an IC50 of 2.6 to 3.1 µM. OSU-03012 was able to induce apoptosis in regular and malignant cell lines while markedly reducing Akt phosphorylation. In xenograft models with the malignant cell line, OSU-03012 was able to inhibit growth by 55% after 9 weeks of oral treatment. Using a mouse schwannoma xenograft model, Clark and colleagues treated animals with trastuzumab, erlotinib, or saline. Both trastuzumab and erlotinib significantly reduced the growth of schwannoma xenografts in comparison with controls ($p < 0.05$). Erlotinib, but not trastuzumab, was noted to induce a significantly higher rate of apoptosis in schwannoma cells ($p < 0.01$) (Clark et al 2008). Erlotinib (150 mg/day) was tested in a series of 11 patients with neurofibromatosis type 2 who had progressive vestibular schwannomas (Plotkin et al 2010). There were no patients with objective MRI responses, although minimal shrinkage was noted in a few. Several patients had stabilization of disease, with a median time to progression of 9.2 months. Hearing responses were not significantly improved in any of the cohort. FRAX597 is a small molecule inhibitor of the group I p21-activated kinases (PAKs), which is discovered via high-throughput screening (Licciulli et al 2013). FRAX597 blocks the back cavity of the ATP binding site of PAKs and was found to inhibit the proliferation of neurofibromatosis type 2-deficient schwannoma cells in culture. In addition, FRAX597 was able to inhibit the growth of schwannoma tumors in an orthotopic model of neurofibromatosis type 2.

Mukherjee and colleagues evaluated sporadic and neurofibromatosis type 2-related schwannomas for the presence of platelet-derived growth factor receptor (PDGFR) and c-kit receptors to assess potential sensitivity to imatinib mesylate, a tyrosine kinase inhibitor of PDGFR and c-kit (Mukherjee et al 2009). Increased expression and activation of PDGFR-alpha, PDGFR-beta, and c-kit receptors was noted. Imatinib mesylate was able to inhibit proliferation and anchorage-dependent growth of neurofibromatosis type 2-null HEI-193 schwannoma cells. In addition, imatinib was able to induce apoptosis in a dose-dependent manner. Similar work by Altuna and colleagues noted expression of PDGFR in 67.5% of vestibular schwannoma samples (Altuna et al 2011). After treatment with imatinib (5 or 10 µM), there was downregulation of phospho-PDGFR. In addition, the use of imatinib induced a dose-dependent increase in G1 percentage (61.6% to 70.7% and 74%; at 5 or 10 µM, respectively), during cell cycle analysis. Imatinib was also able to induce a dose-dependent growth inhibition in colony formation assays using cell lines and cultures derived from fresh tumor tissue. Similar studies by Yener and colleagues evaluated the effect of imatinib treatment on the angiogenic activity of neurofibromatosis type 2-associated and sporadic schwannomas, using a corneal angiogenesis assay (Yener et al 2012). There was significant expression of PDGF-A and -B, as well as PDGFR-α and -β in the tumor tissues. Imatinib was able to significantly reduce the angiogenic potential of both sporadic and neurofibromatosis type 2-associated schwannomas, based on the results of the corneal assay.

Work by Ferguson and coworkers evaluated the activity of sunitinib malate, a selective tyrosine kinase inhibitor that targets c-Kit, PDGFR, and VEGFR, in a murine tumor model of plexiform neurofibromas (Ferguson et al 2016). Sunitinib was able to reduce the Erk1/2 phosphorylation in neurofibroma cells, as well as reduce the size of plexiform neurofibromas and the rate of apoptosis, in comparison to control mice.

Because of the increased activity of the RAS pathway, inhibitors of downstream targets such as RAS-mitogen-activated protein kinase (MEK) have been developed. Dombi and colleagues reported a phase I trial of selumetinib, an oral selective inhibitor of MEK1 and MEK2, in children with neurofibromatosis type 1 with inoperable plexiform

neurofibromas (Dombi et al 2016). There were 24 patients treated; the maximum tolerated dose was 25 mg/m^2 -- approximately 60% of the adult dose. There were confirmed partial responses (shrinkage > 20%) in 17 of 24 patients (71%). In mouse model experiments, 12 of 18 mice (67%) had tumor shrinkage. This drug has not yet been applied to patients with sporadic neurofibromas.

Jakacki and colleagues performed a phase II trial of pegylated interferon alfa-2b in young patients with neurofibromatosis type 1 and unresectable plexiform neurofibromas (Jakacki et al 2016). They treated 82 evaluable patients (median age 10 years old); fatigue and behavioral issues were the most common toxicities. Four patients had imaging responses with tumor shrinkage, whereas another 3 patients had improvement in symptoms. The median time to progression was 29.4 months versus 11.8 months for a placebo arm in a previous trial (P = .031). The use of this drug has not yet been reported in patients with sporadic neurofibromas.

Outcomes

The overall prognosis for survival and intact neurologic function for patients with sporadic schwannomas is relatively good. In most cases, these are benign, slow-growing, encapsulated tumors with a limited capacity for infiltration and destruction of surrounding tissues. Studies evaluating the natural history and growth rates of vestibular schwannomas support this viewpoint. Approximately 40% to 60% of tumors treated conservatively do not enlarge during the period of observation (Wazen et al 1985; Thomsen and Tos 1990; Bederson et al 1991; Nedzelski et al 1992; Macfarlane and King 1995; Rosenberg 2000; Swan 2000; Nutik and Babb 2001; Al Sanosi et al 2006). Of those tumors that do enlarge, 75% to 80% grow at a rate of 0.9 mm to 2 mm per year (Rosenberg 2000). The growth rate may be even slower in elderly patients. In addition, there is a small subgroup of patients (4% to 12%) wherein the tumor will spontaneously involute during long term follow-up (Luetje 2000). When an operation is required for a vestibular schwannoma, a complete resection is considered curative (Jackler and Pitts 1990; Macfarlane and King 1995). The recurrence rate after gross total removal is only 1% to 2% in most large series. Complications of surgery include perioperative mortality (0.5% to 7%), general neurologic sequelae (0.6% to 1.3%), and gait imbalance (up to 9% at 1 year) (Swan 2000). If the resection is incomplete, the residual tumor may have a slower growth rate than the preoperative mass (Wazen et al 1985). Although, in up to 44% of cases, tumor will recur within 7 years, often requiring further surgery or other treatment modalities (El-Kashlan et al 2000). Further growth was persistent once the incompletely resected tumors showed evidence of development. After treatment for a vestibular schwannoma, 70% of patients are able to return to work within 4 months, with another 25% eventually returning at a later date (Jackler and Pitts 1990). However, other authors feel the percentages are lower, with a range of 9% to 38% of all operated patients unable to return to work (Swan 2000). Data have demonstrated that the length of the tumor-cochlear nerve contact is an accurate predictor of hearing outcome (p = 0.0365). Large tumors had longer lengths of contact, resulting in more stretch and extension of the nerve, and a greater chance of hearing loss. This parameter correlated more closely to hearing outcome than tumor diameter (Yong et al 2008).

A study evaluated the quality of life in patients with vestibular schwannomas treated with surgical resection or radiotherapy, or followed by observation (Di Maio and Akagami 2009). Patients treated with radiotherapy or followed by observation did not have any significant changes in quality of life throughout the follow-up period. There were some mild trends for improvement in quality of life for the surgical cohort with tumors less than or equal to 3 cm in size, out to 24 months.

The prognosis for trigeminal schwannomas, as well as those of other cranial nerves, is not as favorable. It is more difficult to achieve a complete resection of these tumors, due to problems such as inadequate surgical exposure, involvement of the cavernous sinus, encasement of blood vessels, and adherence to the brainstem (Miller 1988; Pollack et al 1989; Samii et al 1995; Strauss and Post 1995; Bulsara et al 2008). For trigeminal tumors, the complete resection rate is 70% to 80% in modern series. Recurrence is rare after total extirpation. However, in cases with residual tumor, progression usually occurs within 3 years.

The prognosis for spinal schwannomas is excellent in most cases. The complete resection rate is 85% to 90% in modern series (Seppala et al 1995b; Safavi-Abbasi et al 2008). Recurrence is extremely uncommon after complete resection. Following subtotal removal, recurrence develops in 50% to 55% of patients, often after several years. Reoperation is clinically indicated in only 18% of patients with recurrent tumor (Seppala et al 1995b). The survival of patients with spinal schwannomas is similar to the general population.

For patients with sporadic spinal neurofibromas, the prognosis is also excellent, with a complete resection rate of 90%

or better (Seppala et al 1995a). Recurrence is rare after gross extirpation. However, the survival of these patients is reduced compared to that of the general population.

The prognosis is significantly less favorable for patients with malignant schwannomas (Sordillo et al 1981; Ducatman et al 1986; Cashen et al 2004; Gupta and Maniker 2007). These tumors grow more rapidly and are less amenable to complete resection than typical schwannomas, due to an increased capacity for infiltration of surrounding tissues. In a series of 165 patients with malignant schwannomas of various sites, 60% had no evidence of neurofibromatosis type 1 (Sordillo et al 1981). After radical surgery, 58% of the nonneurofibromatosis type 1 group had local recurrence of disease. Of those patients with recurrent tumors, 52% developed distant metastases, mainly to lung, liver, and bone. The 5-year survival rate for the cohort was 47%. In a study of patients with malignant peripheral nerve sheath tumors, 9% of the nonneurofibromatosis type 1 cohort developed distant metastases, and had a 5-year survival rate of 53% (Ducatman et al 1986). In a report of 80 patients with malignant schwannomas of the peripheral nerves, the functional outcome and survival were similar between patients with neurofibromatosis type 1 and those with nonneurofibromatosis type 1-related tumors (Cashen et al 2004). After aggressive treatment with maximal surgical resection, radiotherapy, and chemotherapy, the survival at 11 years was 85%. A series of 205 patients with malignant peripheral nerve sheath tumors from a single institution had a disease-specific morality rate of 43% at 10 years (Anghileri et al 2006). Higher grade tumors were more likely to have distant metastases, but not a significantly worse survival rate.

Complications of schwannomas vary depending on the location and size of the tumor. In general, the most frequent complications are permanent deficits of the parent nerve and surrounding cranial or spinal nerves, as well as symptoms and signs caused by brainstem or spinal cord compression. The vast majority of patients with vestibular schwannomas are left with some degree of hearing loss in the involved ear as a result of damage from the tumor and treatment (Jackler and Pitts 1990; Glasscock et al 1993; Macfarlane and King 1995; Sanna et al 1995; Samii and Matthies 1997a; Battista 2009). Overall, less than 10% of patients have functional hearing after surgical resection. The most significant prognostic factor for preservation of hearing may be the presence or absence of severe adhesions at the interface between the cochlear nerve and the tumor (Moriyama et al 2002). Another factor that appears to impact on hearing preservation is tumor size (Jacob et al 2007). Tumors less than 1 cm in diameter had the best chance of hearing preservation. However, a review from Duke suggests that with meticulous technique, even large tumors (diameter of 2.1 cm to greater than 4.1 cm) can be completely or near-completely resected, with some degree of hearing preservation (Wanibuchi et al 2009). In their series of 54 patients, 41 patients underwent complete resection (75.9%), with an overall hearing preservation rate of 53.7%.

Although the facial nerve is anatomically intact after surgery in 90% of large tumors and almost 100% of small tumors (ie, intracanalicular and small cisternal), many patients have facial weakness (Jackler and Pitts 1990; Moulin et al 1995; Taha et al 1995; Samii and Matthies 1997b). The degree of facial weakness can vary; 70% of patients with large tumors, 50% of those with medium tumors, and 30% of those with small tumors have neuropraxia of the facial nerve after resection. The weakness is permanent in 30% of cases involving large tumors and 10% of cases involving small and medium-sized tumors. However, more recent series suggest a larger percentage of patients with large tumors can have preserved facial nerve function (75% to 80%) after a retrosigmoid exposure, alone or in combination with a translabyrinthine approach (Anderson et al 2005). More recent reports are in agreement that the retrosigmoid approach is excellent for preservation of hearing and facial nerve function (Samii et al 2006). Some authors recommend aggressive, early nerve reconstruction in patients with facial nerve discontinuity (Samii and Matthies 1997b). Using various methods of reconstruction of the severed nerve, more than 70% of patients can achieve satisfactory results (Samii and Matthies 1997b). Vertigo is a common problem postoperatively, but is usually transient; persistent vertigo is rare. Vertigo occurs more often with small tumors and typically resolves after several weeks to months. On occasion, patients have persistent cerebellar dysmetria as a result of tumor compression of the brainstem or cerebellar retraction during surgery. Impairment of the trigeminal nerve or nerves of the jugular complex (IX, X, XI) can rarely be persistent after treatment of large tumors. Other uncommon complications of schwannomas include hydrocephalus, intratumoral hemorrhage, subarachnoid hemorrhage, rapid cyst expansion, and malignant degeneration (Miller 1988; Jackler and Pitts 1990; Macfarlane and King 1995; Strauss and Post 1995; Pirouzmand et al 2001). Hydrocephalus usually occurs with tumors greater than 3 cm in size and may be present at diagnosis or postoperatively. Permanent shunting should be considered for patients with persistent, symptomatic, postoperative hydrocephalus (Pirouzmand et al 2001). Most patients with preoperative hydrocephalus (78%) will not require a permanent shunt after aggressive resection). It is extremely rare for a sporadic schwannoma to degenerate into a malignant tumor. This complication usually occurs with tumors from patients with neurofibromatosis type 1 or

neurofibromatosis type 2. Malignant peripheral nerve sheath tumors can result in distant metastases, including deposits in the lungs and brain (Park et al 2007).

Special considerations

Pregnancy

Pregnancy does not affect the clinical behavior of schwannomas or neurofibromas.

Anesthesia

There are concerns regarding the presence or absence of elevated intracranial pressure during the induction, maintenance, and emergence from anesthesia that are common to surgical therapy of any brain tumor (LaSala et al 1991; Cucchiara et al 1995). In schwannoma patients who have elevated intracranial pressure, agents that produce excessive sedation and ventilatory depression should be avoided because these could exacerbate intracranial pressure. Hypotonic fluids should also be avoided whenever possible. During the induction and maintenance of anesthesia, agents that minimize hypertension, cerebral vasodilation and blood flow, cerebral metabolic rate, chest wall rigidity, and hypercapnia should be chosen (LaSala et al 1991; Cucchiara et al 1995).

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**References especially recommended by the author or editor for general reading.

ICD and OMIM codes

ICD codes

ICD-9:
Malignant neoplasm of connective and other soft tissue site unspecified: 171.9
Benign neoplasm of cranial nerves: 225.1

ICD-10:
Malignant neoplasm of connective and other soft tissue site unspecified: C49.9
Benign neoplasm of cranial nerves: D33.3

ICD-O:
Neurofibroma, NOS: M9540/0
Schwannoma, NOS: M9560/0

Profile

Age range of presentation

19-44 years
45-64 years
65+ years

Sex preponderance

female>male, >1:1

Family history

none

Heredity

none

Population groups selectively affected

none selectively affected

Occupation groups selectively affected

none selectively affected

Differential diagnosis list

other primary cerebellopontine angle tumors
cysts
vascular malformations
aberrant normal vascular structures
metastatic lesions
meningiomas
epidermoid inclusion cyst
arachnoid cyst
exophytic brainstem gliomas
ependymomas
choroids plexus papillomas
schwannomas of cranial nerve 9
schwannomas of cranial nerve 5
schwannomas of cranial nerve 7
schwannomas of cranial nerve 10
schwannomas of cranial nerve 11
jugular foramen paragangliomas
lipomas
metastases
aneurysm
malformations
aberrant lops of normal blood vessels
tuberculomas
cysticercosis
Meniere disease
vestibular tumors
chondromas
chordomas
astrocytomas
dermoids
teratomas
syringomyelia
multiple sclerosis
transverse myelitis
spondylosis
herniated disc
infection
Lyme disease
syphilis
malignant peripheral nerve sheath tumors
desmoid tumors
granular cell tumors
nerve sheath myxomas
lymphangiomas
myoblastomas

Associated disorders

Acoustic neuroma

Other topics to consider

Molecular diagnosis of brain tumors

Neurofibromatosis type 1
Neurofibromatosis type 2
Noise-induced hearing loss
Radiation plexopathy
Subjective tinnitus
Tumors of the skull base
Vestibular schwannoma