Current Concepts in Management of Meningiomas and Schwannomas

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Intracranial schwannomas and tumors of the meninges have been reported since the eighteenth century [1,2]. These extra-axial lesions lent themselves to clinical detection by presenting overt and focal changes in appearance and function of the harboring patient. The earliest diagnosis of meningiomas during life occurred by causing hyperostotic changes to the overlying skull. The first presumptive case of a vestibular schwannoma can be dated back to autopsy findings by Sandifort in 1777 in which he documented a small body adherent to the right auditory nerve, as related by Cushing [3]. Since their initial discovery, these often-benign lesions have shared a parallel metamorphosis in their management. The goal of this article is to provide a review of the current literature surrounding the mainstays of therapy for these lesions.

Meningiomas and schwannomas are the two most common extra-axial intracranial tumors in adults. Meningiomas account for approximately 25% to 30.1% of all intracranial tumors diagnosed in the United States [4–7]. Data collected from the Central Brain Tumor Registry between 1998 and 2002 reflect trends in meningioma demographics that have shown only modest changes since 1990. These trends include a female age-specific incidence of 6.01 per 100,000 person-years compared with a male age-specific incidence of 2.75 per 100,000 person-years. Although the classic description associates these tumors with middle-aged women, it may be misleading because the median age at diagnosis for these tumors is 64 years.

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and the age-specific incidence increases with each consecutive 10-year age cohort [7,8].

Intracranial nerve sheath tumors compose 8% to 10% of all intracranial tumors [7,9,10]. Schwannomas, which compose the vast majority of these lesions, are the second most common extra-axial intracranial tumor. The male-to-female age-specific incidence ratio (1.01:1) is far less skewed than for meningiomas. These lesions also show a defined peak in incidence during the fifth and sixth decades of life [7].

**Pathogenesis**

*Menigiomas*

Tumorigenesis of meningiomas is presumed to be multifactorial and likely the result of exogenous and endogenous factors. Among the earliest theories regarding their etiology was a causal relationship with head trauma, as first suggested by Cushing [11] in 1922 and then more assertively published in 1938 [12]. Although this suggestion has been supported with isolated reports and case-control studies, it has been refuted by others [13–17]. The seemingly conflicting data leave us without definitive proof of a causal relationship between head injury and subsequent development of intracranial meningiomas [18]. The best-proven external factor with a pathogenic role is radiation. Numerous reports have shown meningiomas to occur in treatment fields associated with low doses of radiation. This concept gained wide acceptance after Modan and colleagues [19] reported a fourfold increase in the incidence of meningiomas among children treated with the Kienbock-Adamson protocol for tinea capitis, a low-dose radiation treatment protocol targeting the scalp that has since been replaced by pharmaceutic alternatives. Higher doses of radiation have been associated with a decrease in the temporal delay to discovery of meningiomas [20,21]. Less convincing supporting data exist for other exogenous factors including viral infection.

Endogenous factors involved in tumorigenesis include molecular alterations found in meningiomas and the ambiguous role of endogenous hormones in tumor development. Meningiomas were among the first solid tumors evaluated by cytogenetics. They were found to have a chromosomal aberration on the long arm of chromosome 22 in 50% to 72% of cases, which involved the tumor suppressor NF2 gene loci in up to 60% of sporadic meningiomas [22–25]. The presence of the NF2 gene product, schwannomin/merlin, in 26% of one series, confirms the lack of universal deletion and underscores the notion that non-NF2 mechanisms are also important [26,27]. Of interest, the absence in reduction of NF2 protein levels may be as high as 72% in some histologic subtypes of meningiomas [28]. Other chromosomal aberrations and genetic abnormalities, including the loss of other tumor suppressor genes (DAK-1, CDKN2A), oncogene activation, and telomerase reactivation, are being implicated in the tumorigenesis of
Meningiomas and the progression toward malignant behavior with accrual of these changes [26].

An almost 2:1 female preponderance of meningiomas reported in the literature and a strong association with breast cancer led to initial interest in the role of sex hormones in the development and progression of meningiomas. Investigation has revealed that tumors expressing progesterone receptors behave in a more benign clinical fashion and are less likely to recur. Tumors expressing estrogen receptor or lacking progesterone receptor expression display more frequent genotypic alterations and karyotype abnormalities consistent with more aggressive meningiomas [29,30]. Although the use of steroid hormone receptor antagonists as targets of therapy was initially successful in mice experiments and promising to a limited potential in humans, it now seems less promising after no benefit was seen in a double-blinded, placebo-controlled phase III study [30,31].

Schwannomas

Schwannomas are slow-growing peripheral nerve sheath tumors that arise distal to the oligodendroglial–Schwann cell myelination transition. Our understanding of these lesions’ pathogenesis has been forwarded by the evaluation of the molecular and genetic changes found in neurofibromatosis 2 (NF2). The \( NF2 \) gene was localized to chromosome 22q12 through genetic linkage analysis [32]. Subsequent genetic and physical mapping led to the discovery of the \( NF2 \) gene by two independent groups in 1993 [33,34]. This region of DNA encodes a 595–amino acid protein product termed “merlin” (for moesin-ezrin-radixin-like protein) or schwannomin, and it functions as a tumor suppressor. Mutations of the \( NF2 \) gene have been found not only in schwannomas associated with NF2 but also in sporadic cases [35–37]. Extensive screening of vestibular schwannomas, however, has not yielded a universal detection of mutations of the \( NF2 \) gene locus, suggesting that additional mechanisms for inactivation of the tumor suppressor may exist [38].

Clinical presentation

Meningiomas

Meningiomas are among the most diverse of all intracranial lesions, presenting with a vast assortment of symptoms, diagnostic imaging results, and histology. The duplicitous nature of these lesions and their ability to mimic diagnostic identifying features of other intracranial pathology have garnered respectful monikers such as the “great masquerader.” Meningiomas originate from arachnoid (meningotheelial) cap cells, which in general are associated with regions containing the trilamellar meninges. Lesions occurring in obscure locations such as the ventricular system can thus be explained by the presence of these cap cells within the tela choroidea. The most common locations of meningiomas, in descending order of frequency, are convexity
(19%–34%), parasagittal (18%–25%), sphenoid and middle cranial fossa (17%–25%), frontal base (10%) and posterior fossa (9%–15%), cerebellar convexity (5%), cerebellopontine angle (2%–4%), intraventricular (1%–5%), and clivus (<1%) [20,39–41].

Meningiomas present in one of four ways, determined by size and location of the tumor [42,43]. With the advent of CT/MRI diagnostic capabilities, meningiomas are being discovered more frequently in an incidental fashion. Indeed, meningiomas represent the most common incidentally detected intracranial neoplasm, accounting for one third of such tumors [39,44]. Ten percent of patients present in this manner, typically asymptomatic with slow or no tumor growth; however, one study of 40 patients revealed tumor growth in 33% and found 10% of patients became symptomatic [44,45]. The second group, accounting for upwards of 50% of patients, may present due to disruption of cortical electrophysiology and present with seizures. Meningiomas may also cause general symptoms of raised intracranial pressure, directly through tumor size and indirectly through associated hemorrhage, edema, obstructive hydrocephalus, and dural venous sinus obstruction. Finally, these tumors may cause neurologic deficits because of neural compression. The clinical presentation in these patients is determined by tumor location and size. Typical clinical presentations have been extensively described in the literature, the most common of which are outlined in Table 1.

Schwannomas

These typically benign tumors may be encountered incidentally but more commonly present to clinical attention secondary to neurologic dysfunction from local mass effect. Some tumors may display a more profound global neurologic effect when cerebrospinal fluid dynamics are altered. Intracranial schwannomas, like their spinal counterparts, show a predilection for involvement of the sensory division of nerves. In order of decreasing frequency, schwannomas arise most commonly from the vestibular component of the eighth nerve (>90%), sensory division of the trigeminal nerve (0.8%–8%), facial nerve (1.9%), nerves of the jugular foramen (2.9%–4%), hypoglossal nerve, extraocular nerves, and the olfactory nerve [46–50]. Because of their intimate relationship with regional cranial nerves, brainstem, and cerebellum, schwannomas may become symptomatic even as relatively small tumors. Conversely, their slow growth rates may mask the insidious progression of neurologic deficits, allow neural elements to deform without a direct loss of function, or both. Typical clinical presentations of intracranial schwannomas are reviewed in Table 2.

Treatment

In the interests of brevity, the microsurgical and radiosurgical treatment results for meningiomas and vestibular schwannomas are discussed the
following sections. These approaches and the associated results can be generally translated to other more rare tumors such as facial or trigeminal schwannomas.

**Microsurgical management**

There is today nothing in the whole realm of surgery more gratifying than the successful removal of a meningioma with subsequent perfect functional recovery… —Harvey Cushing [11]

Surgical resection of acoustic neuromas and meningiomas has been the mainstay of treatment. Several compelling arguments favor surgery: (1) seemingly difficult tumors can sometimes be removed safely; (2) surgery secures a tissue diagnosis—occasionally, a tumor thought to be a meningioma on imaging is determined to be a different lesion; and (3) most meningiomas and acoustic neuromas are benign tumors, and a “cure” can be achieved by
complete resection. Advanced microsurgical and skull-based techniques have led to reduced morbidity and more thorough resections of meningiomas and acoustic neuromas. Despite these advances, gross total resections cannot always be accomplished without placing the patient at significant risk of morbidity and mortality. The goal of surgery should always be to preserve the quality of the patient’s life, even if it means leaving residual tumor.

**Microsurgery results**

**Meningiomas**

The measures used to review operative results in meningioma surgery include radiographic parameters (including recurrence rates) and clinical-based outcomes of morbidity and mortality. In 1957, Simpson [51] retrospectively reviewed the postoperative course of 265 patients who had meningiomas, 55 of whom experienced recurrences (21%). A recurrence rate of 9% was seen in patients who had a grade I excision, a recurrence rate of 19% was seen for grade II excisions, 29% for grade III, and 44% for grade IV (Table 3). The extent of surgical resection is the most important factor in the prevention of recurrence.

Although complete resection is generically the fundamental goal in surgery for these benign lesions, deliberate incomplete resection is often

<table>
<thead>
<tr>
<th>Grade</th>
<th>Extent of resection</th>
<th>Recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Gross total resection of tumor, dural attachments, and abnormal bone</td>
<td>9%</td>
</tr>
<tr>
<td>II</td>
<td>Gross total resection of tumor, coagulation of dural attachments</td>
<td>19%</td>
</tr>
<tr>
<td>III</td>
<td>Gross total resection of tumor without resection or coagulation of dural attachments or its extradural extensions</td>
<td>29%</td>
</tr>
<tr>
<td>IV</td>
<td>Partial resection of tumor</td>
<td>44%</td>
</tr>
<tr>
<td>V</td>
<td>Simple decompression</td>
<td></td>
</tr>
</tbody>
</table>

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Table 2
Intracranial schwannomas: typical clinical presentation

<table>
<thead>
<tr>
<th>Schwannoma</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibular</td>
<td>Unilateral sensory hearing loss, tinnitus, disequilibrium</td>
</tr>
<tr>
<td>Trigeminal</td>
<td>Trigeminal nerve dysfunction (numbness, pain), headache, diplopia, hearing loss/tinnitus</td>
</tr>
<tr>
<td>Facial</td>
<td>Hearing loss, facial paralysis (may be acute), facial pain, hemifacial spasm, tinnitus, vertigo</td>
</tr>
<tr>
<td>Jugular foramen</td>
<td>Cranial nerve palsies (IX, X, XI)</td>
</tr>
<tr>
<td>Accessory nerve</td>
<td>Chronic neck and shoulder pain, muscle spasms</td>
</tr>
<tr>
<td>Hypoglossal</td>
<td>Headache, cranial nerve dysfunction (IX, X, XI), limb weakness</td>
</tr>
</tbody>
</table>

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Table 3
Simpson’s classification of the extent of resection of intracranial meningiomas

undertaken to minimize associated morbidity. This practice is especially true with regard to petroclival, clinoidal, and tentorial-based tumors to reduce related cranial nerve morbidity, and in posterior parasagittal lesions with incomplete obstruction of the superior sagittal sinus to preserve its patency. Inherent to this, recurrence rates of these tumors are higher; the highest recurrence rates (>20%) are found in patients who have sphenoid wing meningiomas, followed by those who have parasagittal meningiomas (8%–24%) and suprasellar meningiomas (5%–10%) [41]. These findings show that the site of tumor origin and its operative accessibility may limit the potential for complete resection and thus serve as a secondary factor influencing recurrence rate [52,53]. Other factors that correlate with an increased recurrence rate include histopathologic findings of increased mitosis, focal necrosis, nuclear pleomorphism, prominent nucleoli, syncytial tumors, and the presence of brain invasion [54–56]. These findings (except brain invasion) have been incorporated into the World Health Organization classification of meningiomas and denote changes toward malignancy.

The surgical morbidity and mortality associated with resection of these lesions has dramatically decreased since initial undertakings at the turn of the twentieth century. This decrease has been a result of improved diagnostic imaging, introduction of microsurgical techniques and image guidance, and better perioperative critical/medical care. Even in the best hands, however, mortality rates remain at 1% to 14% [57–62]. Factors that increase mortality include poor preoperative clinical condition, compressive symptoms from tumor, old age, incomplete tumor removal, pulmonary embolism, and intracranial hemorrhage [58].

Morbidity associated with meningioma surgery has been cataloged and critically reviewed and should be clustered into two broad categories. The low-risk group includes tumors that provide an easy corridor for access and that are spatially removed from cranial nerves, brainstem, and vital cerebrovascular anatomy. Examples of such tumors include cerebral and cerebellar convexity tumors, lateral- and middle-third sphenoid wing meningiomas, and anterior-third parasagittal and falcine meningiomas. In most cases, convexity meningiomas are amenable to complete resection and improved operative mortality rates [63,64]. Neurologic sequelae associated with these resections typically manifest secondary to compromise of adjacent cerebrovascular structures, immediate postoperative edema, and epilepsy [57]. In one study, convexity meningioma recurrence-free rates at 5, 10, and 15 years were 93%, 80%, and 68%, respectively [65]. Several investigators have reported low mortality rates (0%–3%) and morbidity manifesting as permanent neurologic deficit in 10% of patients [66–68]. Similarly, relatively low rates of postoperative-increased morbidity can be found with anterior-third parasagittal and falcine meningiomas.

The high-risk group of meningiomas includes tumors of the skull base, tentorial-based tumors, foramen magnum meningiomas, and parasagittal...
lesions associated with the middle third of the superior sagittal sinus. Basal
tumors are often intimately associated with cranial nerves and proximal ce-
rebral vessels, thereby making the approach to these lesions a formidable
challenge. With resection of skull-base tumors, permanent neurologic deficit
ascribed to cranial nerve dysfunction has been reported in a wide range
(18%–86%) [69]. The highest of these complication rates is typically associ-
ated with petroclival or cavernous sinus meningiomas, especially in cases in
which a complete resection is performed [70–72]. Subtotal resection for de-
compression, even with tumors of the cavernous sinus, can be performed
safely, although recurrence rates are naturally higher.

Schwannomas (vestibular)

The first reported surgical removal of a vestibular schwannoma was per-
formed by Sir Charles Ballance [73] in 1894. Although alive and well over
a decade later, the patient suffered ipsilateral facial paralysis and numbness,
two neurologic sequelae that were not uncommon during initial undertak-
ings for removal of these tumors. During this time period, Dandy [74] re-
ported the operative mortality to be 67% to 84%. Through improved
surgical methodology and technique, Cushing was able to markedly de-
crease the mortality rates associated with operative management of these le-
sions, thereby ushering neurosurgeons and neuro-otologists into the modern
era of surgery for acoustic neuromas. Since that time, the introduction of the
operating microscope, more sensitive diagnostic imaging, and intraoperative
facial and cochlear monitoring has steadily reduced the morbidity and mor-
tality associated with resection of these lesions. In a meta-analysis of 16
studies including 5005 patients undergoing microsurgery for sporadic unilat-
eral vestibular schwannomas, it was reported that tumor resection was com-
plete in 96% of cases, with a mortality rate of 0.63%. The most common
non-neurologic complication was cerebrospinal fluid leak, which occurred
in 6.0% of patients [75].

With an expectant small mortality and major morbidity rate, the more
common end points for evaluation of a successful surgery have turned to
preservation of facial nerve function and auditory function. In 1985, House
and Brackmann [76] developed what has become the most widely accepted
measurement of facial nerve function (Table 4). Detailed evaluation of indi-
vidual large series shows that preservation of facial nerve function is in-
versely proportional to tumor size. Indeed, when evaluating facial nerve
preservation after resection of intracanalicular lesions alone, multiple stud-
ies have reported 100% postoperative grade I House-Brackmann function
[77–81]. Resection of small tumors (<2.0 cm), medium-sized tumors (2.0–
3.9 cm), and large tumors (>4.0 cm) was respectively associated with a
95% to 97%, a 61% to 73%, and a 28% to 57% preservation of grade
I to II House-Brackmann function [82–84]. In reviewing the relative rates
of facial nerve dysfunction, the suboccipital and translabyrinthine ap-
proaches afford comparable and excellent results compared with the middle
fossa approach in which increased manipulation of the superiorly located facial nerve in the internal auditory canal may account for a higher risk to facial nerve function [84–86].

Similarly, the importance of preservation of serviceable ipsilateral hearing has become paramount. The translabyrinthine approach, through its destruction of the otic capsule, is not compatible with hearing preservation [85]. Resection of purely intracanalicular tumors is associated with a 57% to 82% preservation of ipsilateral serviceable auditory function [77,79]. Risk to serviceable auditory function is directly related to tumor size. In 1988, Gardner and Robertson [87] compiled results of multiple operative series and found hearing preservation in 131 of 394 patients, although only 5 of these patients had tumors larger than 3 cm. Subsequent studies have reported retention of functional ipsilateral hearing in 29% to 60% of cases, primarily with tumors less than 3 cm, and a precipitous decline in hearing preservation rates in cases with larger tumors [78,79,88,89]. The objective criteria for the designation of serviceable hearing vary between these studies and may account for the disparity in rates of hearing preservation.

### Table 4

<table>
<thead>
<tr>
<th>Grade</th>
<th>Function</th>
<th>Gross</th>
<th>Motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal facial function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Mild dysfunction</td>
<td>Slight weakness noticeable on close inspection</td>
<td>Forehead: moderate-to-good function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have slight synkinesis</td>
<td>Eye: complete closure with minimal effort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At rest, normal symmetry and tone</td>
<td>Mouth: slight asymmetry</td>
</tr>
<tr>
<td>III</td>
<td>Moderate dysfunction</td>
<td>Obvious but not disfiguring difference between the two sides</td>
<td>Forehead: slight-to-moderate movement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Noticeable but not severe synkinesis, contracture, or hemifacial spasm</td>
<td>Eye: complete closure with effort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At rest, normal symmetry and tone</td>
<td>Mouth: slightly weak with maximum effort</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately severe dysfunction</td>
<td>Obvious weakness and/or disfiguring asymmetry</td>
<td>Forehead: none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At rest, normal symmetry and tone</td>
<td>Eye: incomplete closure</td>
</tr>
<tr>
<td>V</td>
<td>Severe dysfunction</td>
<td>Only barely perceptible motion</td>
<td>Mouth: asymmetric with maximum effort</td>
</tr>
<tr>
<td>VI</td>
<td>Total paralysis</td>
<td>No movement</td>
<td>No movement</td>
</tr>
</tbody>
</table>

Radiosurgical management

Radiosurgery may be used for patients who have recurrent or residual tumors or as a primary treatment in patients unwilling or unable to undergo surgery and who possess a lesion with the typical imaging characteristics of an acoustic neuroma or meningioma. Radiosurgery for meningiomas is usually performed with the gamma knife. Occasionally, modified linear accelerators or proton beam can be used. Patients who have atypical findings on MRI or CT should undergo surgery to obtain a histologic diagnosis. This practice is critical because when gamma knife radiosurgery (GKRS) is used to treat tumors on imaging characteristics alone, the risk of an incorrect diagnosis may be as high as 2% [90].

Location plays a pivotal role in the selection of the appropriate treatment modality. Convexity meningiomas are usually treated with open surgery because they are amenable to complete resection. Acoustic neuromas, skull-base (including cavernous sinus and petroclival) and parasagittal meningiomas, on the other hand, are ideal lesions for radiosurgery due to their anatomy and associated surgical morbidity and mortality.

Residual tumor attached to still-patent vascular or neural structures can be targeted using radiosurgery, allowing less radical microsurgical resection and a lower incidence of morbidity. For radiosurgery, a distance of at least 3 to 4 mm between the tumor and the optic apparatus is ideal. With thin-cut stereotactic planning MRI and shielding, radiosurgery can be used to treat lesions within 2 mm of the optic apparatus. The authors tend to favor early treatment of acoustic neuromas or skull-base meningiomas rather than a “watch and wait” approach because of the favorable benefit-to-risk profile of GKRS.

Radiosurgery results

Meningiomas

Neuroimaging outcomes. The authors have treated more than 300 meningiomas at the University of Virginia since 1989. The most recent evaluation of the authors’ material included 206 patients who had meningiomas treated with GKRS, with a follow-up of 1 to 6 years. This evaluation included 142 patients treated for residual disease and 64 patients treated with GKRS primarily. Tumor volume ranged from 1 to 32 cm³. These patients received an average of 38 Gy maximum dose (range, 20–60 Gy) and an average margin dose of 14 Gy (range, 10–20 Gy). Radiographic follow-up was available for 151 patients. Of the evaluated patients, 94 (63%) showed a tumor volume decrease of at least 15% and 40 (26%) showed no change in size, corresponding to an 89% tumor control rate. Tumor growth was noted in 17 patients (11%). The authors now have long-term follow-up (10–21 years) of 31 meningiomas treated with GKRS. Two thirds of these tumors have shrunk significantly or remained stable. Among these tumors are those
in which only the vascular supply for the tumor (ie, the nutritive vessel) was targeted. Such targeting has resulted in significant tumor shrinkage and lasting effect, even in the long-term.

The results of other centers are similar (Table 5) [90–101]. The University of Pittsburgh group recently reported long-term results in 85 patients whose meningiomas were treated with GKRS. With a median follow-up of 10 years, they reported that 53% of the tumors decreased in size and 40% were stable in size, corresponding to a 93% tumor control rate [102]. Kreil and colleagues [103], with a median follow-up of 7.9 years, similarly reported on 200 patients treated with GKRS for meningiomas and found that 56.5% of meningiomas demonstrated a decreased volume and 42.5% showed stable tumor volumes. Pollock and colleagues [104] compared the efficacy of GKRS with that of microsurgery for the treatment of meningiomas that had an average diameter less than 35 mm. They concluded that progression-free survival after radiosurgery is equivalent to that after resection of a Simpson grade 1 tumor and was superior to that after Simpson grade 2, 3, or 4 resections, confirming the efficacy of GKRS, especially in tumors in which gross total resection is difficult to achieve due to anatomic constraints.

**Atypical and malignant meningioma outcomes.** Atypical and malignant meningiomas usually demonstrate recurrence and aggressive growth regardless of the treatment modality (ie, extirpation, radiosurgery, or radiation therapy). Although GKRS appears to work very well for typical meningiomas, some centers have reported on the outcomes of atypical and malignant meningiomas treated with GKRS. The results are generally consistent with those for typical meningiomas, with a high rate of tumor control and a low rate of complications. However, the outcomes for atypical and malignant meningiomas can be less favorable due to the more aggressive nature of these tumors.

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### Table 5

Outcome of radiosurgery for meningiomas

<table>
<thead>
<tr>
<th>Author (year) [Reference]</th>
<th>N</th>
<th>Follow-up (mo)</th>
<th>Decrease (%)</th>
<th>Stable (%)</th>
<th>Increase (%)</th>
<th>Complications (%)</th>
<th>Improved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pendl et al (1997) [98]</td>
<td>97</td>
<td>48</td>
<td>39</td>
<td>56</td>
<td>5</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Liscak et al (1999) [94]</td>
<td>67</td>
<td>2–60</td>
<td>52</td>
<td>48</td>
<td>0</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Roche et al (2000) [93]</td>
<td>80</td>
<td>12–79</td>
<td>31</td>
<td>64</td>
<td>5</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Lee et al (2002) [99]</td>
<td>159</td>
<td>2–145</td>
<td>34</td>
<td>60</td>
<td>6</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Roche et al (2003) [92]</td>
<td>32</td>
<td>28–188</td>
<td>12</td>
<td>88</td>
<td>—</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>Kondziolka (2003) [102]</td>
<td>85</td>
<td>120</td>
<td>53</td>
<td>40</td>
<td>7</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Liscak et al (2004) [100]</td>
<td>176</td>
<td>36</td>
<td>73</td>
<td>25</td>
<td>2</td>
<td>15.5</td>
<td>63</td>
</tr>
<tr>
<td>Kreil et al (2005) [103]</td>
<td>200</td>
<td>60–144</td>
<td>57</td>
<td>42</td>
<td>2</td>
<td>3</td>
<td>42</td>
</tr>
<tr>
<td>Pollock (2005) [101]</td>
<td>49</td>
<td>58</td>
<td>59</td>
<td>41</td>
<td>—</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>Steiner &amp; Sheehan a</td>
<td>151</td>
<td>6–252</td>
<td>63</td>
<td>26</td>
<td>11</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

*Abbreviation: —, n/a.

a Unpublished data from the author’s series.*
the results for atypical and malignant meningiomas are less favorable. In a study from the University of Pittsburgh, Harris and colleagues [105] reported 5-year progression-free survival rates of 83% and 72% for atypical and malignant meningiomas, respectively. Malik and colleagues [106] reported less favorable results, reporting 5-year actuarial control rates of 49% in atypical meningiomas and 0% in malignant meningiomas. Ojemann and colleagues’ [107] results were similar to those of Malik and colleagues [106]; they reported a 5-year progression-free survival rate of 26% in patients who had malignant meningiomas treated with GKRS, although outcomes were better in smaller tumors and in young patients. Survival rates, as opposed to control rates, have also been reported for patients after GKRS of atypical and malignant meningiomas. Five-year overall survival rates vary between 59% and 76% in patients who have atypical meningiomas and between 0% and 59% in patients who have malignant meningiomas [105,107,108].

**Radiation-induced meningioma outcomes.** It is well known that fractionated radiation therapy can induce meningiomas. The incidence of radiation-induced tumors following fractionated radiation therapy is 1.9% in 20 years. Some centers (including the authors’) have had limited yet favorable early experience with radiosurgical treatment of radiation-induced tumors. For example, the Mayo Clinic group recently reported a 100% 5-year local tumor control rate for 16 patients who had radiation-induced tumors [109]. The median follow-up from the Mayo Clinic report was only 40.2 months. Although it is too early to know whether such an approach is prudent, the concept of treating radiation-induced meningiomas with radiosurgery may have some interesting implications regarding the pathogenesis of intracranial tumors.

**Clinical outcomes following radiosurgery.** Many patients who present for management of meningiomas, especially skull-base lesions, present with neurologic deficits such as cranial nerve dysfunction. It is therefore important not only to evaluate outcomes with respect to tumor control but also clinical outcomes. GKRS is regularly reported to be associated with improved cranial nerve function after treatment of skull-base meningiomas. Pollock and Stafford [110], for example, reported that 12 of 38 patients who presented with cranial neuropathies associated with cavernous sinus meningiomas had improvement in cranial nerve function on follow-up. Roche and colleagues [93] also reported on clinical outcomes in patients who had cavernous sinus meningiomas treated with GKRS. They reported that 23 of 54 patients who had oculomotor palsy improved or completely recovered and that 7 of 13 patients who had trigeminal neuralgia improved or completely recovered. Roche and colleagues [92] reported similar success in GKRS-treated petroclival meningiomas: 13 of 32 patients treated with GKRS for petroclival meningiomas had clinical improvement in cranial
nerve dysfunction. Kreil and colleagues [103] reported that 96% of patients who had skull-base meningiomas treated with GKRS had improved or stable neurologic status, with improvement noted in a broad range of areas including vision and other cranial nerve functions, hemiparesis, ataxia, vertigo, seizures, and exophthalmus.

**Vestibular schwannomas**

*Neuroimaging outcomes.* At the University of Virginia’s Lars Leksell Gamma Knife center, the authors and colleagues have treated 400 patients who had vestibular schwannomas. One hundred fifty-three of these patients who had greater than 12 months’ follow-up have been reported [111]. Radiosurgery was the primary treatment for 96 patients and the adjuvant treatment (following microsurgery) in 57 patients. The volume of the treated tumors ranged from 0.02 to 18.3 cm³.

Of the patients treated primarily with GKRS, 81% (78 patients) experienced a decrease in tumor size (Fig. 1), 12% had no change, and 6% had an increase in size. Among the 78 patients who had decreased tumor size, the decrease was greater than 50% in 20 patients. It is the authors’ policy to not consider decreases in volume of less than 15% as significant. Radiologic follow-up for these patients ranged from 1 to 10 years.

Of the 57 patients treated with GKRS after microsurgery, 65% obtained a decrease in tumor size, 25% had no change, and 10% had an increase in tumor size. Among the 37 patients who had a decrease in the size of their tumors, the decrease was greater than 50% in 12 patients. The outcome in terms of postradiosurgical volume reduction in patients who had prior microsurgery is worse compared with the outcome in those who were treated primarily with radiosurgery. This difference is likely a result of the increased difficulty with accurate targeting in those who underwent prior microsurgery. Of note, although the authors’ experience with treating large vestibular schwannomas is small (n = 19), they have observed a 95% tumor control rate in these patients following radiosurgery. Other centers report similar rates (89%–100%) of tumor control (ie, no change or a decrease in the size of the tumor) in patients (Table 6) [111–118].

The Karolinska group included evaluation of radiographic changes other than size [116]. The most common change was loss of central enhancement within the tumor on contrasted MRI or CT studies. This loss of central enhancement occurred in 70% of patients and was typically observed within 6 to 12 months of treatment. These changes, however, were reversible. Another change that was observed and that the authors have often seen is a transient increase in the size of the tumor during the first 6 months after radiosurgery. This change is commonly seen in tumors that then regress to their original size or smaller.

*Clinical outcomes following radiosurgery.* In the vestibular schwannoma patients treated at the University of Virginia, five had transient changes in
trigeminal sensation and three had facial paresis. One of the patients who had facial weakness was operated on shortly after radiosurgery and was lost to follow-up. Another patient recovered completely in 6 weeks, and the third has nearly completely recovered at 10 months. Of the patients who had useful hearing before GKRS, 58% retained their hearing following radiosurgery, 42% experienced some degree of deterioration, and 31% lost useful hearing. Most hearing changes were observed at the 2-year checkup, and additional auditory changes were observed as late as 8 years post radiosurgery.

Fig. 1. Vestibular schwannomas. Of the patients treated primarily with GKRS, a decrease in tumor size was seen in 81% (78 patients). (A) Pretreatment T1WI with contrast. (B) Post-treatment T1WI with contrast (12 months post-treatment).
Previously published prevalence of cranial neuropathies at other centers were 17% at Karolinska and 29% at Pittsburgh for facial paresis, which in most cases was transient or mild. The trigeminal nerve was affected in a variety of ways in 33% at Pittsburgh, most commonly a mild hypoesthesia. Recent complication rates at these institutions are comparable to those at the authors’ center. The authors have not seen an instance of cerebellar edema or hydrocephalus requiring spinal fluid diversion following GKRS for vestibular schwannomas, but these complications have been reported elsewhere [111,116].

Summary

The initial management of a patient presenting with radiographic evidence of a typically benign extra-axial neoplasm is a complex and evolving process. As we approach an era in which the molecular processes underlying neoplastic transformation and proliferation become more clearly delineated, new chemotherapeutic agents targeting these processes will broaden our armamentarium with which we can target these tumors. Exciting frontiers, such as treatment of meningiomas with cyclo-oxygenase-2 inhibitors, should be embraced with cautious optimism. Enthusiasm generated by successful in vitro and nonprimate experiments in the treatment of meningiomas with antihormonal therapy and hydrosurea has met significant obstacles in the transition to efficacy in human clinical trials. We are hopeful that in the near future we may be enlightened with a chemobiologic treatment advance that is comparable to the contributions brought to meningioma and schwannoma management by radiosurgery over the past several decades.

Patients presenting with asymptomatic, small meningiomas may be best managed conservatively with a trial of expectant management and close surveillance with sequential MRI. In the treatment of these lesions, conservative management may be undertaken with a period of observation for

### Table 6

Outcome of radiosurgery for vestibular schwannomas

<table>
<thead>
<tr>
<th>Author (year) [Reference]</th>
<th>No. of patients who had follow-up imaging studies</th>
<th>Mean follow-up (mo) of 12</th>
<th>Tumor increased (%)</th>
<th>Tumor unchanged or decreased (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noren et al (1993) [116]</td>
<td>209</td>
<td>minimum</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>Foote et al (1995) [117]</td>
<td>35</td>
<td>16</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Kwon et al (1998) [112]</td>
<td>63</td>
<td>52</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Prasad et al (2000) [118]</td>
<td>153</td>
<td>51</td>
<td>7</td>
<td>93</td>
</tr>
<tr>
<td>Flickinger et al (2001) [113]</td>
<td>190</td>
<td>30</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>Bertalanffy et al (2001) [114]</td>
<td>40</td>
<td>36</td>
<td>9</td>
<td>91</td>
</tr>
</tbody>
</table>
3 to 12 months before any definitive treatment decision is made [119]. Meningiomas presenting in symptomatic patients due to mass effect should generally be resected completely, especially in the subset of patients harboring tumors that are relatively low risk for surgical complication. Meningioma surgery in the elderly (≥65 years old) has been performed with rates of morbidity and mortality similar to a control group of younger patients matched for tumor size and location [120]. Thus, age should not be a deterrent for microsurgical treatment. A decision regarding invasive surgical management versus radiosurgery can be influenced by preinterventional clinical performance status of the patient. When the mass effect of high-risk types of tumors extends beyond local cranial nerve dysfunction, surgical debulking becomes an absolute prequel to adjuvant radiosurgical methods, even when a complete resection is not practical. The greatest amount of controversy exists in treatment of small (<3 cm) skull-base lesions presenting due to focal neurologic signs and symptoms solely from cranial nerve dysfunction. Radiosurgery advocates, in support of primary radiosurgical intervention, note the efficacy of radiosurgical methods in controlling tumor growth and emphasize the high rates of immediate postoperative morbidity associated with attempted surgical resection of these lesions. Supporters of complete surgical resection stress the importance of cure being the ultimate goal, as opposed to control of the disease. They also question the legitimacy of long-term control of tumor growth with radiosurgery, citing the lack of long-term follow-up. A third approach involves the combination of these therapeutic modalities. The benefits from immediate surgical decompression of the cranial nerves with tumor debulking as a pretreatment adjunct to radiosurgical therapy for residual tumor is suggested as a synergistic, rather than mutually exclusive, way to approach the management of these difficult skull-base lesions [121].

The management of small and medium-sized vestibular schwannomas emphasizes the fundamental questions that are brought about in the management of skull-base meningiomas. These lesions arise in the cerebellopontine angle where, even at a small size, they may cause profound effects on cranial nerve function. Surgical management of these lesions allows a cure (recurrence-free) in 92% to 100% of patients undergoing a complete resection, with a small rate of major morbidity and mortality [120–126]. The effectiveness of primary radiosurgical management in the control of tumor growth is indisputable in most patients. Even a tumor with marginal mass effect that extends beyond local cranial nerve involvement may be managed exclusively with radiosurgery. This management is possible because of the large subset of treated tumors that decreases in tumor volume after treatment (see Fig. 1). Monitoring trends in management over the last 2 decades has shown a precipitous decrease in the number of patients undergoing operative intervention, commensurate with a proportional increase in the number of patients treated with radiosurgical methods. The reasons for this are multifactorial, the least of which may be any true indication that
radiosurgery is a better alternative than microsurgery for treatment of these lesions. The once-patriarchal patient–physician interaction has been replaced with one of informed patient decision making. Patients are gaining a skeptical understanding of treatment paradigms through use of the Internet and health care advertising, and the wave of enthusiasm for minimally invasive surgery and noninvasive therapeutic modalities is swelling. This, in conjunction with third-party payors helping formulate health care delivery strategies and protocols has placed the management of vestibular schwannomas at the whim of supply and demand economics, rather than a true shift toward superior outcomes. As with any new therapy that comes to the attention of the medical community, this initial crest in interest will subside and an equilibrium will be reached that emphasizes the unique benefits of microsurgery and radiosurgery in the management of these lesions and of their respective definitive niches. At this juncture, providing patients ready accessibility to treatment modalities and education regarding the objectives, risks, and success rates of each will help clarify which management strategy is most suitable for patients on an individual basis.

References


