

Intracranial meningiomas: an overview of diagnosis and treatment

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✓Meningiomas are extraaxial central nervous system tumors most often discovered in middle to late adult life, and are more often seen in women. Ninety percent of meningiomas are benign, 6% are atypical, and 2% are malignant. Most patients in whom a meningioma is diagnosed undergo resection to relieve neurological symptoms. Complete resection is often curative. For the majority of incompletely resected or recurrent tumors not previously irradiated, radiotherapy is administered. Radiotherapy may be administered as either conventional external-beam radiation therapy or stereotactically by linear accelerator, Leksell Gamma Knife, or Cyberknife radiosurgery. Advocates of stereotactic radiotherapy have suggested this therapy in lieu of surgery particularly in high-risk patients, those with meningiomas in eloquent or surgically inaccessible locations, and elderly patients. When the meningioma is unresectable or all other treatments (surgery and radiotherapy) have failed, hormonal therapy or chemotherapy may be considered. Notwithstanding limited data, hydroxyurea has been modestly successful in patients with recurrent meningiomas. (DOI: 10.3171/FOC-07/10/E1)

KEY WORDS • central nervous system tumor • intracranial meningioma • treatment

IN 1614, Felix Plater first described a meningioma in an autopsy report.^{5,15,50,60} A French surgeon, Antoine Louis, published the first report in 1754 that dealt specifically with meningiomas.^{5,15,58,60} In 1847, Virchow described meningiomas as psammonas (sandlike) because of the presence of tumoral granules. In 1864, Bouchard termed meningiomas as epitheliomas, and in 1869 Golgi described them as endotheliomas. In 1922, Harvey Cushing first used the term meningioma. Pathologists subsequently have demonstrated the origin of meningiomas as arachnoid cap cells commonly found in association with arachnoid villi at the dural venous sinuses and veins.^{15,60}

The first case relating prior head trauma to causality of meningioma involved General Leonard Wood, Major General and Chief of Staff of the United States Army.^{40,54} In 1910, Cushing successfully performed surgery on Gen. Wood's parasagittal meningioma.⁴⁰

Hospital-based brain tumor series indicate that the incidence of meningiomas is approximately 20% of all intracranial tumors (the most common nongliar primary intracranial tumor), whereas autopsy-based studies indicate an overall incidence of 30%. Furthermore, 2% of autopsies reveal incidental meningiomas. There is an age-dependent incidence of meningiomas (0.3/100,000 in childhood and

8.4/100,000 in the elderly). Ninety percent of all meningiomas occur in the supratentorial compartment.^{5,15,41,58,60} Intracranial meningiomas are most common in adults in their fourth through sixth decades of life and are rare in children (2% of all meningiomas present in childhood).^{2,4,5,15,41,46,58,60} Meningiomas are more common in African-Americans and in females. There is a 2:1 female to male ratio in intracranial meningiomas.^{5,15,41,58,60} A female preponderance for meningioma correlates with an endogenous hormone level and exogenous hormone replacement in postmenopausal women (in whom an increased incidence of meningioma is seen) as compared with postmenopausal women who have not taken exogenous hormone replacement therapy.^{5,13,15,31,32,41,48,58,60} Increased growth of meningiomas during pregnancy as well as postpartum clinical regression has been reported but remains poorly understood.⁵⁵ Recently, however, no associations with reproductive or hormonal factors were observed in a case-control study of 151 meningiomas in female patients.²⁷ The literature does not support any association between the development of meningiomas and oral contraceptives.¹³

Clinical Presentation

The clinical presentation of meningiomas (Table 1), as is true of all intracranial mass lesions, is dependent on tumor location (Tables 2 and 3).^{5,15,29,41,56,58,60} Meningiomas are most often slow-growing tumors, and symptoms at presentation are rarely precipitous, but more often insidious in

Abbreviations used in this paper: CT = computed tomography; MR = magnetic resonance; NF2 = neurofibromatosis Type 2; PFS = progression-free survival; SWOG = Southwest Oncology Group.

nature. New-onset and slowly evolving headache is common and usually unassociated with other symptoms suggestive of raised intracranial pressure, reflecting the slow growth of these tumors. A protracted history of partial seizures for convexity meningiomas is not uncommon nor is an insidious personality change (easily confused with dementia or depression) in patients with large inferior frontal meningiomas. A number of topographic anatomical tumor syndromes have been defined (Table 3); however, these syndromes are not etiologically specific as a variety of focal intracranial lesions (for example, granulomas, gliomas, and cysts) may present in a similar manner.⁵³

Evaluation of Imaging Studies

Brain imaging with contrast-enhanced CT or MR imaging is the most common method of diagnosing, monitoring, and evaluating response to treatment (Table 4). Plain x-ray films, most often obtained for coincidental indications, may reveal a number of findings characteristic of meningioma including intratumoral calcifications, bone hyperostosis giving rise to a “sunray effect,” a secondary osteolytic lesion, a dilated middle meningeal artery groove, posterior clinoid erosion, suture separation, and a “beaten brass” appearance of the skull.⁵³

Although MR imaging is the imaging technique of choice for glial tumors as it provides more intracranial detail, CT scanning still has an important role in the imaging of meningiomas. The CT scan best reveals the chronic effects of slowly growing mass lesions on bone remodeling. Calcification in the tumor (seen in 25%) and hyperostosis of surrounding skull are features of an intracranial meningioma that can be easily identified on a noncontrast CT scan. Nonetheless, MR imaging reveals a number of characteristics highly suggestive of meningioma and in recent stereotactic radiotherapy articles, MR imaging has been used to operationally define pathological findings.^{10-15,33} These MR imaging findings include a tumor which is dural-based and isointense with gray matter, demonstrates prominent and homogeneous enhancement (> 95%), frequent cerebrospinal fluid/vascular cleft(s), and often an enhancing dural tail (60%). However, approximately 10 to 15% of meningiomas have an atypical appearance on MR images, mimicking metastases or malignant gliomas.⁷ In particular, secretory meningiomas may have a significant amount of peritumoral edema. Cerebral angiography is occasionally performed, often for surgical planning, as meningiomas are vascular tumors prone to intraoperative bleeding.^{5,15,29,41,56,58,60} In some instances preoperative embolization is helpful for operative hemostasis management. Angiographic findings consistent with a meningioma include a dual vascular supply with dural arteries supplying the central tumor and pial arteries supplying the tumor periphery. A sunburst effect may be seen due to enlarged and multiple dural arteries, and a prolonged vascular stain or so-called blushing can be seen, which results from intratumoral venous stasis and expanded intratumoral blood volume.⁵³

There has also been interest in the use of MR spectroscopy to assist in the diagnosis of meningiomas. This modality may be particularly useful in patients unable to undergo a surgery for whatever reason. Creatinine containing peaks in meningioma are 20% that of comparable levels in

TABLE 1
*History and physical findings in patients with intracranial meningioma**

Signs & Symptoms	No. of Patients (%)	
	Benign Meningioma	Malignant Meningioma
patient history		
headache	70 (36)	5 (36)
personality change/confusion	43 (22)	3 (21)
paresis	37 (19)	6 (43)
generalized seizures	36 (19)	1 (7)
visual impairment	30 (16)	4 (29)
focal seizures	29 (15)	2 (14)
ataxia	28 (15)	3 (21)
aphasia	19 (10)	2 (14)
decreased level of consciousness	13 (7)	2 (14)
paresthesia	11 (6)	0 (0)
diplopia	6 (3)	0 (0)
vertigo	2 (1)	0 (0)
decreased hearing	2 (1)	0 (0)
physical findings		
paresis	57 (30)	7 (50)
normal examination	51 (26)	2 (14)
memory impairment	29 (15)	3 (21)
other cranial nerve deficit	21 (12)	0 (0)
visual field deficit	19 (10)	3 (21)
paresthesia	17 (9)	3 (21)
aphasia	17 (9)	1 (7)
papilledema	15 (8)	2 (14)
decreased visual acuity	12 (6)	7 (7)
altered level of consciousness	9 (5)	2 (14)
nyctagmus	6 (3)	0 (0)
decreased hearing	4 (2)	0 (0)

* Based on data from articles by Bondy, De Monte, Jääskeläinen, Longstreth, Rutten, Sanson, Wilson, and their colleagues. Tables 2, 3, and 4 are also based on these tables.

normal brain.⁴² An increase in the choline-containing peaks and the alanine peak have been reported as well.³⁵ A low inositol peak may help distinguish a meningioma from a schwannoma.³⁵ Buhl et al.⁸ reported that greater than 63% of atypical meningiomas had a characteristic lactate peak on preoperative MR spectroscopy.

Although positron emission tomography has not been routinely used in the diagnostic workup and follow-up of patients with meningiomas, it can be useful in cases of skull base meningiomas that are frequently difficult to visualize by using standard CT and MR imaging techniques. Rutten et al.⁵⁶ reported that using positron emission tomography/CT and 2-¹⁸F-fluoro-L-tyrosine, a marker of amino acid transport, maybe a useful in managing meningiomas. These authors showed that 2-¹⁸F-fluoro-L-tyrosine uptake completely overlapped with the MR imaging lesion in 54%, extended beyond the MR imaging lesion in 38%, and were smaller in 8% of the tumors. This technique may be particularly useful in patients who previously underwent radiation therapy.

Meningiomas are also known to have high somatostatin receptor density allowing for the potential use of octreotide brain scintigraphy to help delineate extent of disease.³⁶ This may be particularly useful in distinguishing residual tumor from postoperative scarring in subtotally resected/recurrent tumors.

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TABLE 2
Location of intracranial meningiomas demonstrated by CT scanning

Tumor Location	No. of Meningiomas (%)	
	Benign	Malignant
convexity	60 (34)	7 (50)
parasagittal	39 (22)	4 (29)
sphenoid ridge	30 (17)	3 (21)
lateral ventricle	10 (5)	0 (0)
tentorium	7 (4)	0 (0)
cerebellar convexity	9 (5)	0 (0)
tuberculum sellae	7 (3)	0 (0)
intraorbital	4 (2)	0 (0)
cerebellopontine angle	4 (2)	0 (0)
olfactory groove	6 (3)	0 (0)
foramen magnum	1 (1)	0 (0)
clivus	1 (1)	0 (0)
other	1 (1)	0 (0)
total	179	14

TABLE 3
Clinical syndromes of intracranial meningiomas

Location	Syndrome
parasagittal/parafalcine	simple partial seizures, paraparesis
posterior parasagittal	homonymous hemianopsia
anterior parasagittal	neurobehavioral syndrome
sphenoid wing	visual loss, trigeminal dysfunction, ophthalmoplegia
olfactory groove	anosmia, dementia
suprasellar	bitemporal hemianopia
tentorial	headache, vertigo, ataxia

been identified as an important factor in meningioma tumorigenesis.²⁶ Aside from loss of 22q (the *NF2* gene), loss of 1q, 14q, and 10q occurs in atypical and malignant meningiomas.^{1,26} Additionally, both epidermal growth factor receptor and platelet derived growth factor receptor are overexpressed in meningioma.

There are two rare familial conditions (*NF2* and meningiomatosis), both inherited as autosomal-dominant traits, which predispose patients to developing meningiomas.^{1,26,34}

Rarely (< 1% of all meningiomas) these tumors may occur following either low-dose radiotherapy as was once administered routinely for tinea capitis, or following high-dose radiotherapy as given for glioma or head and neck malignancies.⁵⁷ In both instances, long delays (10 or more years) occur between the administration of radiotherapy and meningioma occurrence and, not infrequently, multifocal tumors develop.

Pathologically, the biological behavior of meningiomas may be predicted by MIB-1 labeling indices, vascular endothelial growth factor receptor expression, quantitative staining of proliferating cell nuclear antigen and expression of Janus tyrosine kinase and signal transducer and activator of transcription proteins.^{14,28,44,62}

Natural History

Authors of several studies have examined the growth rate of incidental meningiomas (that is, meningiomas discovered in an otherwise asymptomatic patient).^{6,17,19,50,52} Findings reported in one study indicated that 12% of meningiomas were diagnosed in patients based on imaging findings and of these patients (12 of 100), one demonstrated progression warranting intervention.⁶ Another observational study of 17 patients with meningiomas demonstrated an annual tumor growth rate of 3.6 mm.¹⁹ In a retrospective study of 60 patients observed for an average of 32 months (6 months–15 years), none became symptomatic because of their tumor.⁵² In 45 of these patients, 35 (48%) showed no tumor growth on imaging performed over 29 months, and 10 (22%) demonstrated tumor growth which progressed an average of 2.4 mm a year (median 47 months of observation). The authors concluded that the majority of asymptomatic meningiomas may be followed safely with serial brain imaging until either the tumor enlarges significantly or becomes symptomatic. A fourth observational study demonstrated that 29% of meningiomas diagnosed (35 of 121) were incidental and asymptomatic.¹⁷ All patients were followed by serial brain imaging and tumor progression was seen in four (11%); however, only one patient devel-

Pathological Characteristics and Molecular Genetics

A variety of pathological subtypes of meningioma have been defined and are outlined in Table 5. Notwithstanding the histological variety of meningiomas, treatment is determined primarily by the World Health Organization classification, a three-tiered system comprised of three grades (meningioma, atypical meningioma, and anaplastic meningioma). Histopathological analysis reveals that meningiomas have the following characteristic array of immunohistological markers: epithelial membrane antigen, vimentin, laminin, fibronectin, carcinogenic embryonic antigen, S100, and keratin. In addition, meningiomas express a variety of cell surface receptors as follows: progesterone, androgen, glucocorticoid, somatostatin, epidermal derived growth factor, insulin-like growth factor-I and -II, transforming growth factor- β , interferon- α , fibroblast growth factor-1, estrogen, prolactin, and platelet-derived growth factor receptor.

The primary chromosomal aberration in meningiomas is monogamy or deletion of chromosome 22.^{1,5,15,26,34,41,58,60} The meningioma gene has been mapped to a region between the myoglobin locus and the *c-sis* protooncogene. Loss of one chromosome 22 occurs in 75% of meningiomas and is the sole chromosomal abnormality in 50%.^{1,26} The loss of chromosome 22 is believed to represent the loss of a putative tumor suppressor gene and thereby results in malignant change. In the majority of patients with sporadic meningiomas, the lost tumor suppressor gene appears to be the *NF2* gene, a 595 amino acid-long protein called merlin or schwannomin that belongs to the band 4.1 superfamily of proteins.^{1,26} Merlin appears to function as a molecular switch regulating cell contacts by binding to actin cytoskeleton and cell proliferation by binding to a transcription factor. Conformational changes determine the activity of merlin. In the closed state merlin is active and functions as a growth suppressor, whereas in the open state merlin is inactive and is growth permissive. Loss of expression for merlin varies by histological subtype of meningioma and is highest in fibrous and transitional tumors and lowest in meningotheliomatous types. Recently, loss of another member of the 4.1 family of proteins, DAL-1 (absent in ~ 50% of all meningiomas), has

TABLE 4
Computed tomography scanning findings in patients with meningioma

Tumor Location	No. of Patients (%)	
	Benign Meningioma	Malignant Meningioma
midline shift	140 (78)	12 (86)
homogenous enhancement	129 (72)	5 (36)
nonhomogenous enhancement	41 (23)	9 (64)
no adjacent hypodensity	86 (48)	0 (0)
mild adjacent hypodensity	55 (31)	2 (14)
moderate adjacent hypodensity	10 (5)	10 (71)
severe adjacent hypodensity	28 (16)	2 (14)
hyperostosis	32 (18)	1 (7)
calcification	49 (270)	0 (0)
fringing*	2 (1)	2 (14)
mushrooming†	0 (0)	8 (57)

* Appearance of the dural tail on CT scanning and MR imaging.

† Refers to the apparent cap and broad short stalk appearance of many meningiomas.

oped symptoms. Noncalcified tumors were more likely to progress (four [36%] of 11) than calcified tumors (zero [0%] of 24). In the fifth and final observational study the authors observed 40 elderly patients with asymptomatic meningiomas; tumor progression was noted in 14 (35%) of these patients; however, only five patients (12%) became symptomatic.⁵⁰

These studies confirm the tenet that many meningiomas grow very slowly and that a decision not to operate is justified in selected asymptomatic patients. As the growth rate is unpredictable in any individual, repeated brain imaging is mandatory to monitor an incidental asymptomatic meningioma. An interval of 6 months after the initial study, followed by images at increasing intervals (as stability is confirmed over the first 1–2 years) appears adequate to assess growth rate and need for intervention.

Treatment for Meningiomas

Surgical Procedures

The treatment of meningiomas is dependent on both patient-related factors (age, performance status, medical comorbidities) and treatment-related factors (reasons for symptoms, respectability, and goals of surgery). In patients who are considered surgical candidates (surgically accessible symptomatic meningiomas), the goal of therapy is total excision.^{5,15,29,41,56,58,60} As with all brain tumors, completeness of resection is determined by early (< 72 hours) postoperative, contrast-enhanced brain imaging using either CT or MR imaging. Brain MR imaging following resection and the histopathological findings at the time of resection constitute the basis for the Simpson grading system, a predictive system for meningioma recurrence (Table 6). Patients with a Simpson Grade 1 meningioma have a 9% 10-year recurrence rate compared with patients with a Simpson Grade 3 meningioma in whom a 29% 10-year recurrence rate is seen. Prognostic variables predictive for survival³⁷ in patients with meningiomas include the extent of resection, histological grade, patient's age, and tumor location.

Mirimanoff et al.⁴⁶ reported recurrence-free survival

TABLE 5
World Health Organization classification of tumors of meningeothelial cell origin

Grade	Tumor Types
I	meningioma meningeothelial (syncytial) transitional fibrous psammomatous angiomatous microcystic secretory clear cell chordoid lymphoplasmocyte-rich metaplastic variants (xanthomatous, myxoid, osseous, cartilaginous)
II	atypical meningioma
III	anaplastic (malignant) meningioma

rates following total resection of 93% at 5 years, 80% at 10 years, and 68% at 15 years. In contrast with partial resection, recurrence-free survival rates dropped to 63, 45, and 9%, respectively. In a study of patients with benign intracranial meningiomas, Jääskeläinen²⁹ found a recurrence rate of 19% at 20 years following complete resection. He reported that in patients with atypical or malignant meningiomas following complete resection, the risk of recurrence was 38% and 78%, respectively, at 5 years.

Radiation Therapy

Radiation therapy should be considered following partial resection of a meningioma and following resection of atypical or malignant meningiomas.^{5,15,20,41,43,58,60} Improving on the recurrence-free survival rates cited by Mirimanoff et al.⁴⁶ (see earlier), Goldsmith et al.²⁰ found an 89% 5-year progression free survival (PFS) with adjunct radiotherapy (median dose 54 Gy) in 140 patients with a partially resected benign meningioma. The 10-year PFS was 77%. Although with radiotherapy the PFS rate for a partially resected meningioma can approach that of a gross-total resection (63% up to 89%), the decision to undertake radiotherapy should be weighed against the potential for symptomatic recurrence (considering the slow growth rate of most meningiomas) in the patient's lifetime, versus potential side effects of radiation (for example, leukoencephalopathy and cognitive symptoms, necrosis, and focal neurological injury).

The use of stereotactic radiotherapy (either single fraction or fractionated) in the management of meningiomas continues to evolve.^{3,18,39,43,47,51} Using the linear accelerator, Leksell Gamma Knife, or Cyberknife, stereotactic radiotherapy has been administered in lieu of external-beam radiotherapy for small (< 35-mm) tumors, which are either recurrent or partially resected. In addition, stereotactic radiotherapy has been used as primary therapy in surgically inaccessible tumors (for example, skull base meningiomas) or in patients deemed poor surgical candidates such as some elderly. The studies reported to date in which the authors used stereotactic radiotherapy for meningiomas involve comparatively small numbers of patients (usually < 100) with relatively short follow-up times (usually < 5

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TABLE 6
Simpson Grading System for meningiomas*

Grade	Definition
1	macroscopic GTR w/ excision of dura, sinus & bone
2	macroscopic GTR w/ coagulation of dural attachment
3	macroscopic resection w/o resection or coagulation of dural attachment
4	STR
5	biopsy

* GRT = gross-total resection; STR = subtotal resection.

years). Notwithstanding these caveats, results of stereotactic radiotherapy compare favorably with external-beam radiotherapy and surgery in select patients with meningioma.^{3,18,39,43,47,51} A majority of patients will obtain disease stabilization, and a small minority of these patients will achieve tumor regression.¹⁶ This is an important point when considering patients for serial observation who will likely need radiotherapy at some juncture for residual/recurrent disease.

Hormonal Therapy

Both epidemiological (female predominance) and biochemical evidence (70% of meningiomas are progesterone receptor positive and 30% are estrogen receptor positive) suggest meningioma growth may be hormone dependent.^{5,15,31,41,58,60} Additionally, approximately 60% of meningiomas show staining of prolactin receptors.^{32,48} As a consequence, a variety of hormonal therapies have been used in the treatment of recurrent benign meningiomas not amenable to further surgery or radiotherapy. The oral progesterone agonist megestrol acetate (Megace) was used in a small trial of nine patients with no observed response.²³ Subsequently, in a trial of 14 patients, the progesterone antagonist mifepristone (RU-486) was used.²⁴ Five objective minor responses were seen though availability of mifepristone limited further study. The SWOG completed a study of mifepristone for unresectable meningiomas (198 total patients of whom 160 were evaluable).²² The results did not support a role for RU-486 compared with placebo (median PFS 10 months in the RU-486 arm and 12 months in the placebo arm). In addition, SWOG reported a Phase II trial of 21 patients with meningioma treated with oral tamoxifen, an estrogen receptor antagonist.²¹ One patient achieved a partial response, two patients had a minor response, and six patients had stable disease for longer than 6 months.

Biotherapy and Chemotherapy

Recombinant interferon- α has been found to inhibit the growth of cultured human meningioma cell lines in vitro.^{33,61} Three small reports, two in abstract form, have been published.^{22,24,45,59,61} In the largest report, six patients with recurrent unresectable and previously irradiated meningiomas were treated. One patient had an objective response and four patients had stable disease for longer than 6 months.

Schrell and colleagues³⁹ demonstrated in vitro that hydroxyurea, an oral chemotherapeutic agent with a variety of antitumoral effects, was a potent inhibitor of cultured meningioma cells by inducing apoptosis. A clinical trial by Schrell et al.⁵⁹ involving four patients, another by Newton et al.⁴⁵ involving 40 patients, and a third trial reported by Mason et al.⁴⁹ involving 20 patients suggested in vivo efficacy (> 80% with stable disease for a median of 20 to 30 months)⁴⁹ (Table 7).

Calcium channel antagonists have a strong inhibitory effect on meningioma growth in culture and are being investigated for their clinical utility in conjunction with chemotherapeutic agents.³⁰ A recent trial of chronic oral temozolomide for surgical and radiotherapy refractory meningiomas failed to demonstrate activity in 16 patients.¹² Similarly, a trial of CPT-11 (irinotecan) in 16 patients with refractory meningiomas failed to show significant activity notwithstanding in vitro work suggesting antimeningioma activity.^{11,25} In another small trial of 16 patients, those with recurrent meningiomas shown to overexpress somatostatin receptors by octreotide scintigraphy were treated with monthly long-acting somatostatin.¹⁰ Thirty-one percent of patients demonstrated a partial imaging-documented response, and 44% achieved PFS at 6 months with minimal toxicity. Somatostatin analogs may offer a novel, relatively nontoxic alternative treatment for patients with recurrent meningiomas.

Multidrug chemotherapy trials for recurrent meningiomas whether aggressive, malignant, or refractory to surgery and radiotherapy are scant.^{9,38} The best-documented chemotherapy regimen (cyclophosphamide, adriamycin, and vincristine) has been used primarily in an adjuvant setting for the treatment of malignant meningiomas; however, without a control group, the results are difficult to interpret.⁹ Other published regimens do not report response rates, duration of response or toxicity data, and therefore should be regarded as investigational.³⁸ Unpublished data from a small number of patients from a Phase II SWOG trial for aggressive meningeal tumors and malignant meningiomas with ifosfamide/mesna did not show initial promise.

TABLE 7
Hydroxyurea for recurrent meningioma*

Authors & Year	No. of Meningiomas (no. benign)	Prior RT	Toxicity in % (> Grade 3)	Response	
				Best	Median TTP
Newton et al., 2000	17 (13)	7	25 (15)	stable disease in 88%	20 mos
Mason et al., 2002	20 (16)	8	15	stable disease in 50%	30 mos

* RT = radiotherapy; TTP = time to progression.

Conclusions

The decision to treat a meningioma is dependent on tumor size and associated symptoms.

Many small incidentally discovered intracranial meningiomas may be observed expectantly. Evidence for meningioma development and growth associated with reproductive and hormonal factors, especially in premenopausal women is not compelling. Contrast-enhanced cranial CT and MR imaging are the predominant imaging techniques used in the diagnosis and management of meningiomas; however, in selected cases, MR spectroscopy and octreotide scintigraphy may be useful. Surgery, when complete and image-verified, results in the best long-term survival and freedom from disease recurrence. Radiotherapy is recommended for tumors incompletely resected or recurrent following initial surgery. Stereotactic radiosurgery is increasingly used both as primary therapy (for example, in an elderly patient with a tumor in an eloquent brain location) and as salvage therapy for recurrent meningioma. Long-term outcome studies, however, are lacking. Hormonal, immunotherapy, and chemotherapy for recurrent meningioma having failed surgery and radiotherapy is only partially effective. Of the agents studied, hydroxyurea appears the most effective. However, there is a paucity of clinical trials on which to make decisions regarding these agents.

In summary, meningiomas are benign extraaxial CNS tumors, which when symptomatic are typically treated with definitive resection. However, small asymptomatic meningiomas may be observed and followed by sequential MR and CT imaging. Radiation therapy is suggested for residual and recurrent disease following surgery and for symptomatic meningiomas in surgically hazardous locations (for example, the cavernous sinus). In elderly patients or high-risk patients who undergo surgery, small meningiomas are increasingly being treated primarily with stereotactic radiotherapy. Several trials of chemotherapeutic and hormonal agents for progressive or recurrent disease have been reported and are ongoing. These studies should be interpreted with caution, as no large cohorts have been studied nor has the therapy been shown to cause regression of disease, and “stability” must be scrutinized carefully, given the natural biology and inherent slow rate of growth of these tumors. Clearly there is a need to develop new biological, genetic, and chemotherapeutic options for recurrent meningiomas that have exhausted surgical and radiation treatment options. Future treatments will likely include gene therapy using viral vectors, biodegradable wafers containing biological response modifiers or chemotherapeutic agents, monoclonal antibodies targeted to meningioma cell surface tumor markers, and small molecules that antagonize surface receptors or ligands involved in cell growth.

References

- Antinheimo J, Sankila R, Carpén O, Pukkala E, Sainio M, Jääskeläinen J: Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas. *Neurology* **54**:71–78, 2000
- Baumgartner JE, Sorenson JM: Meningioma in the pediatric population. *J Neurooncol* **29**:223–228, 1996
- Black PM: Hormones, radiosurgery and virtual reality: new aspects of meningioma management. *Can J Neurol Sci* **24**:302–306, 1997
- Blumenthal D, Berho M, Bloomfield S, Schochet SS Jr, Kaufman HK: Childhood meningioma associated with meningioangiomas. Case report. *J Neurosurg* **78**:287–289, 1993
- Bondy M, Ligon BL: Epidemiology and etiology of intracranial meningiomas: a review. *J Neurooncol* **29**:197–205, 1996
- Braunstein JB, Vick NA: Meningiomas: the decision not to operate. *Neurology* **48**:1459–1462, 1997
- Buetow MP, Buetow PC, Smirniotopoulos JG: Typical, atypical, and misleading features in meningioma. *Radiographics* **11**:1087–1106, 1991
- Buhl R, Nabavi A, Wolff S, Hugo HH, Alfke K, Jansen O, et al: MR spectroscopy in patients with intracranial meningiomas. *Neur Res* **29**:43–46, 2007
- Chamberlain MC: Malignant meningiomas: adjunct combined modality therapy. *J Neurosurg* **84**:733–736, 1996
- Chamberlain MC, Glantz MJ, Fadul CE: Recurrent meningioma: salvage therapy with sandostatin. *Neurology* **69**:969–973, 2007
- Chamberlain MC, Tsao-Wei D, Groshen S: Salvage chemotherapy with CPT-11 for recurrent meningioma. *J Neurooncol* **78**:271–276, 2006
- Chamberlain MC, Tsao-Wei D, Groshen S: Temozolomide for treatment resistant recurrent meningioma. *Neurology* **62**:1210–1212, 2004
- Claus EC, Black PM, Bondy ML, Calvocoressi L, Schildkraut JM, Wiemels JL, et al: Exogenous hormone use and meningioma risk. *Cancer* **110**:471–476, 2007
- Cobb MA, Husain M, Andersen BJ, Al-Mefty O: Significance of proliferating cell nuclear antigen in predicting recurrence of intracranial meningioma. *J Neurosurg* **84**:85–90, 1996
- De Monte F: Current management of meningiomas. *Oncology (Williston Park)* **9**:83–91, 96, 99–101, 1995
- DiBiase SJ, Kwok Y, Yovino S, Arena C, Naqvi S, Temple R, et al: Factors predicting local tumor control after gamma knife stereotactic radiosurgery for benign intracranial meningiomas. *Int J Radiat Oncol Biol Phys* **60**:1515–1519, 2004
- Firsching RP, Fischer A, Peters R, Thun F, Klug N: Growth rate of incidental meningiomas. *J Neurosurg* **73**:545–547, 1990
- Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD: Gamma Knife radiosurgery of imaging-diagnosed intracranial meningioma. *Int J Radiat Oncol Biol Phys* **56**:801–806, 2003
- Go RS, Taylor BV, Kimmel DW: The natural history of asymptomatic meningiomas in Olmsted County, Minnesota. *Neurology* **51**:1718–1720, 1998
- Goldsmith BJ, Wara WM, Wilson CB, Larson DA: Postoperative irradiation for subtotally resected meningiomas. *J Neurosurg* **80**:195–201, 1994
- Goodwin JW, Crowley J, Eyre HJ, Stafford B, Jaecle KA, Townsend JJ: A phase II evaluation of tamoxifen unresectable or refractory meningiomas: a Southwest Oncology Group Study. *J Neurooncol* **15**:73–77, 1993
- Grunberg SM, Rankin C, Townsend C, Ahmadi J, Feun L, Fredericks R, et al: Phase III double-blind randomized placebo-controlled study of mifepristone (RU-486) for the treatment of unresectable meningioma. *Proc Am Soc Clin Oncol* **20**:222, 2001 (Abstract)
- Grunberg SM, Weiss M: Lack of efficacy of megestrol acetate in the treatment of unresectable meningioma. *J Neurooncol* **8**:61–65, 1990
- Grunberg SM, Weiss MH, Spitz IM, Ahmadi J, Sadun A, Russell CA, et al: Treatment of unresectable meningiomas with the anti-progesterone agent mifepristone. *J Neurosurg* **74**:861–866, 1991
- Gupta V, Su YS, Samuelson CG, Liebes LF, Chamberlain MC, Hofman FM, et al: Irinotecan: A potential new chemotherapy for atypical or malignant meningiomas. *J Neurosurg* **106**:455–462, 2007
- Gutmann DH, Donahoe J, Perry A, Lemke N, Gorse K, Kitiniyom K, et al: Loss of DAL-1, a protein 4.1-related tumor suppressor, is an important early event in the pathogenesis of meningiomas. *Hum Mol Genet* **9**:1495–1500, 2000

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27. Hatch EE, Linet MS, Zhang J, Fine HA, Shapiro WR, Selker RG, et al: Reproductive and hormonal factors and risk of brain tumors in adult females. **Int J Cancer** **114**:797–805, 2005
28. Ho DM, Hsu CY, Ting LT, Chiang H: Histopathology and MIB-1 labeling index predicted recurrence of meningiomas: a proposal of diagnostic criteria for patients with atypical meningioma. **Cancer** **94**:1538–1547, 2002
29. Jääskeläinen J: Seemingly complete removal of histologically benign intracranial meningioma: late recurrence rate and factors predicting recurrence in 657 patients. A multivariate analysis. **Surg Neurol** **26**:261–469, 1986
30. Jensen RL, Orogitano TC, Lee YS, Weber M, Wurster RD: In vitro growth inhibition of growth factor-stimulated meningioma cells by calcium channel antagonists. **Neurosurgery** **36**:365–374, 1995
31. Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ: Sex steroid hormone exposures and risk for meningioma. **J Neurosurg** **99**:848–853, 2003
32. Jimenez-Hakim E, el-Azouzi M, Black PM: The effect of prolactin and bombesin on the growth of meningioma-derived cells in monolayer culture. **J Neurooncol** **16**:185–190, 1993
33. Kaba SE, DeMonte F, Bruner JM, Kyritsis AP, Jaecle KA, Levin V, et al: The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. **Neurosurgery** **40**:271–275, 1997
34. King A, Gutmann DH: The question of familial meningiomas and schwannomas: NF2B or not to be? **Neurology** **54**:4–5, 2000
35. Kinoshita Y, Yokota A: Absolute concentrations of metabolites in human brain tumors using in vitro proton magnetic resonance spectroscopy. **NMR Biomed** **10**:2–12, 1997
36. Klutmann S, Bohuslavizki KH, Brenner W, Behnke A, Tietje N, Kröger S, et al: Somatostatin receptor scintigraphy in postsurgical follow-up examinations of meningioma. **J Nucl Med** **39**:1913–1917, 1998
37. Kondziolka D, Lunsford D, Coffey RJ, Flickinger JC: Stereotactic radiosurgery of meningiomas. **J Neurosurg** **74**:552–559, 1991
38. Kyritsis AP: Chemotherapy for meningiomas. **J Neurooncol** **29**:269–272, 1996
39. Lee JY, Niranjan A, McNerney J, Kondziolka D, Flickinger J, Lunsford LD: Stereotactic radiosurgery providing long-term control of cavernous sinus meningiomas. **J Neurosurg** **97**:65–72, 2002
40. Ljunggren B: The case of General Wood. **J Neurosurg** **56**:471–474, 1982
41. Longstreth WT Jr, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD: Epidemiology of intracranial meningioma. **Cancer** **72**:639–648, 1993
42. Lowry OH, Berger SJ, Chi MM, Carter JG, Blackshaw A, Outlaw W: Diversity of metabolic patterns in human brain tumors. I. High energy phosphate compounds and basic composition. **J Neurochem** **29**:959–977, 1977
43. Lunsford DL: Contemporary management of meningiomas: radiation therapy as an adjuvant and radiosurgery as an alternative to surgical removal? **J Neurosurg** **80**:187–190, 1994
44. Magrassi L, De-Fraga C, Conti L, Butti G, Infuso L, Govoni S, et al: Expression of the JAK and STAT superfamilies in human meningiomas. **J Neurosurg** **91**:440–446, 1999
45. Mason WP, Gentili F, Macdonald DR, Hariharan S, Cruz CR, Abrey LE: Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. **J Neurosurg** **97**:341–346, 2002
46. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL: Meningioma: analysis of recurrence and progression following neurosurgical resection. **J Neurosurg** **62**:18–24, 1985
47. Morita A, Coffey RJ, Foote RL, Schiff D, Gorman D: Risk of injury to cranial nerves after gamma knife radiosurgery for skull base meningiomas: experience in 88 patients. **J Neurosurg** **90**:42–50, 1999
48. Muccioli G, Ghé C, Faccani G, Lanotte M, Forni M, Ciccarelli E: Prolactin receptors in human meningiomas: characterization and biological role. **J Endocrinol** **153**:365–3731, 1997
49. Newton HB, Slivka MA, Stevens C: Hydroxyurea chemotherapy for unresectable or residual meningioma. **J Neurooncol** **49**:165–170, 2000
50. Niuro M, Yatsushiro K, Nakamura K, Yoshihiro K, Kuratsu J: Natural history of elderly patients with asymptomatic meningiomas. **J Neurol Neurosurg Psychiatry** **68**:25–28, 2000
51. Ojemann SG, Sneed PK, Larson DA, Gutin PH, Berger MS, Verhey L, et al: Radiosurgery for malignant meningioma: results in 22 patients. **J Neurosurg** **93** (3 Suppl):62–67, 2000
52. Olivero WC, Lister JR, Elwood PW: The natural history and growth rate of asymptomatic meningiomas: a review of 60 patients. **J Neurosurg** **83**:222–224, 1995
53. Osborne AG: Meningiomas and other nonglial neoplasms, in **Diagnostic Neuroradiology**. St. Louis: Mosby Year Book, 1994, pp 579–625
54. Phillips LE, Koepsell TD, van Belle G, Kukull WA, Gehrels JA, Longstreth WT Jr: History of head trauma and risk of intracranial meningioma: population-based case-control study. **Neurology** **58**:1849–1852, 2002
55. Roelvink NCA, Kamphorst W, Van Alphen HA, Rao BR: Pregnancy-related primary brain and spinal tumors. **Arch Neurol** **44**:209–215, 1987
56. Rutten I, Cabay JE, Withofs N, Lemaire C, Aerts J, Baart V, et al: PET/CT of skull base meningiomas using 2–18F-fluoro-L-tyrosine: initial report. **J Nucl Med** **48**:720–5, 2007
57. Sadezki S, Flint-Richter P, Ben-Tal T, Nass D: Radiation-induced meningioma: a descriptive study. **J Neurosurg** **97**:1078–1082, 2002
58. Sanson M, Cornu P: Biology of meningiomas. **Acta Neurochir (Wein)** **142**:493–505, 2000
59. Schrell UMH, Rittig MG, Anders M, Koch UH, Marschalek R, Kiesewetter F, et al: Hydroxyurea for the treatment of unresectable and recurrent meningiomas. II. Decrease in the size of meningiomas in patients treated with hydroxyurea. **J Neurosurg** **86**:845–852, 1997
60. Wilson CB: Meningiomas: genetics, malignancy, and the role of radiation in induction and treatment. The Richard C. Schneider Lecture. **J Neurosurg** **81**:666–675, 1994
61. Wöber-Bringöl Ç, Wöber C, Marosi C, Prayer D: Interferon-alfa-2b for meningioma. **Lancet** **345**:331, 1995
62. Yamasaki F, Yoshioka H, Hama S, Sugiyama K, Arita K, Kurisu K: Recurrence of meningiomas. Influence of vascular endothelial growth factor expression. **Cancer** **89**:1102–1110, 2000

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