Intracerebral Meningiomas

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Opinion statement

Meningiomas are extra-axial brain tumors of middle to late adult life, and they have a female predominance. Overall, 90% of meningiomas are benign, 6% are atypical, and 2% are malignant. Most patients diagnosed with a meningioma decide to have it removed surgically and are advised to do so based on their neurologic symptoms. Complete surgical resection is usually curative. For incompletely resected or recurrent tumors not previously irradiated, radiotherapy is administered. Radiotherapy may be administered as conventional external beam irradiation or stereotactically. Stereotactic radiotherapy, as linear accelerator or gamma-knife radiosurgery is increasingly used. Advocates of stereotactic radiotherapy have suggested this therapy in lieu of surgery particularly for poor surgical risk patients, patients with meningiomas in eloquent or surgically inaccessible locations, and patients of advanced age. When the meningioma is unresectable or all other treatments (surgery, radiotherapy) have failed, immunochemotherapy may be considered. Hydroxyurea, interferon-alpha, tamoxifen, and mifepristone have been modestly successful in patients with recurrent meningiomas, whereas cyclophosphamide, adriamycin, and vincristine, ifosfamide/mesna, or adriamycin/dacarbazine have been administered to patients with aggressive or malignant meningiomas.

Introduction

Meningiomas are extra-axial brain tumors of middle to late adult life that have a female predominance. Overall, 90% of meningiomas are benign, 6% are atypical, and 2% are malignant [1,2••]. Most patients diagnosed with a meningioma decide to have it removed surgically and are advised to do so based on their neurologic symptoms [2••,3,4•,5–7,8••,9,10,11•, Class II]. Complete surgical resection is usually curative. For incompletely resected or recurrent tumors not previously irradiated, radiotherapy is administered [2••,8••, 9,10,11•, Class II]. Radiotherapy may be administered as conventional external beam irradiation or stereotactically. Stereotactic radiotherapy (SRT), such as linear accelerator (LINAC) or gamma-knife radiosurgery, is increasingly used [8••,9,10,11•, Class II]. Advocates of SRT have suggested this therapy in lieu of surgery particularly for poor surgical risk patients, patients with meningiomas in eloquent or surgically inaccessible locations, and patients of advanced age [9,10,11•, Class II]. When the meningioma is unresectable or all other treatments (surgery, radiotherapy) have failed, immunochemotherapy may be considered [12,13•,14, 15,16•,17,18•, Class II]. Hydroxyurea, interferon-alpha, tamoxifen, and mifepristone have been modestly successful in patients with recurrent meningiomas, whereas cyclophosphamide, adriamycin and vincristine, ifosfamide/mesna, or adriamycin/dacarbazine have been administered to patients with aggressive or malignant meningiomas [10, Class II].

In 1614, Plater first described a meningioma in an autopsy report. A French surgeon, Antoine Louis, published the first report that dealt specifically with meningiomas. In 1847, Virchow described meningiomas as *psammonas* (sand-like) because of the presence of tumoral granules. In 1864, Bouchard termed *meningiomas epitheliomas*, followed by Golgi's description in 1869 in which he used the term *endotheliomas*. In 1922, Cushing first used the term *meningioma*. Pathologists subsequently demonstrated the origin of meningiomas as arachnoid cap cells commonly found associated with arachnoid villi at the dural venous sinuses and veins [1,2••].

Hospital-based brain tumor series indicate that the incidence of meningiomas is approximately 20% of all intracranial tumors, whereas population-based studies

Table 1. History and physical findings in patients with meningiomas

Signs and symptoms	Benign meningiomas		Malignant meningiomas	
	Patients, *n*	Patients, %	Patients, *n*	Patients, %
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
Decreasing 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
Nystagmus	6	3	0	0
Decreased hearing	4	2	0	0

indicate an overall incidence of two to three individuals per 100,000 [1]. Meningiomas have a two-to-one female-to-male ratio, are most common in adults in their fourth, fifth, and sixth decade of life, and are rare in childhood (2% of all meningiomas) [1,2••,8••,19–21].

The clinical presentation of meningiomas (Table 1), as is true of all intracranial mass lesions, is dependent on tumor location (Table 2) [1,2••,8••,20,21]. A number of topographic syndromes have been defined; however, these syndromes are not etiologically specific, because a variety of focal intracranial lesions (*eg*, granulomas, gliomas, and cysts) may present in a similar manner [1,2••,20,21]. A variety of pathologic subtypes of meningioma has been defined and outlined in Table 3. Brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is the most common method of diagnosing and observing response to treatment (Table 4).

The primary chromosomal aberration in meningiomas is monosomy or partial deletion of chromosomal 22 [22,23]. The meningioma gene has been mapped to a region between the myoglobin locus and the *c-sis* proto-oncogene. Loss of one chromosome 22 occurs in 75% of meningiomas and is the sole chromosomal abnormality in 50% of meningiomas. 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 neurofibromatosis type-2 gene. Aside from loss of chromosome 22q (the neurofibromatosis type-2 gene), loss of chromosome 1q, 14q, and 10q occurs in atypical and malignant meningiomas. Rarely (<1% of all meningiomas), meningiomas may occur after low-dose radiotherapy as administered for tinea capitis or after high-dose radiotherapy as given for glioma [24]. In these instances (radiation-induced meningiomas), long delays (10 or more years) occur between the administration of radiotherapy and meningioma occurrence. There are in addition two rare familial conditions (neurofibromatosis type-2 and meningiomatosis), inherited as autosomal dominant traits, that predispose patients to developing meningiomas [25].

Several studies have examined the growth rate of incidental meningiomas (meningiomas discovered in an otherwise asymptomatic patient) [3,4•,5–7, Class III].

Table 2. Location of meningiomas in patients demonstrated by computerized tomography

Tumor location	Benign meningiomas		Malignant meningiomas	
	Patients, *n*	Patients, %	Patients, *n*	Patients, %
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. World Health Organization classification of tumors and meningiothelial cell origin

- Meningioma
  - Meningiothelial (syncytial)
  - Transitional
  - Fibrous
  - Psammomatous
  - Angiomatous
  - Microcystic
  - Secretory
  - Clear cell
  - Chordoid
  - Lymphoplasmacyte-rich
  - Metaplastic variants (xanthomatous, myxoid, osseous, cartilagenous, and others)
- Atypical meningioma
- Anaplastic (malignant) meningiomas
  - Variants of meningioma
  - Papillary

One report indicated that 12% of all patients diagnosed radiographically with meningiomas were observed and of these patients (12 of 100), one patient demonstrated progression warranting intervention [4•]. Another observational study of 17 patients demonstrated an annual growth rate of 3.6 mm [6]. In a retrospective study of 60 patients observed an average of 32 months (6 months to 15 years), none became symptomatic from their tumor [3]. In 45 of these patients, 35 (48%) showed no tumor growth on imaging over 29 months, and 10 patients (22%) demonstrated tumor growth that progressed an average of 2.4 mm per year (median of 47 months of observation). The authors concluded that the majority of asymptomatic meningiomas may be monitored safely with serial brain imaging until the tumor enlarges significantly or becomes symptomatic. A fourth observational study demonstrated that 29% (35 of 121) of meningiomas diagnosed were incidental and asymptomatic [5]. All patients were monitored via serial brain imaging, and tumor progression was seen in four patients (11%); however, only one patient developed symptoms. Noncalcified tumors were more likely to progress (five of 11 patients [36%]) than calcified tumors (none of 24 patients [0%]). The fifth and final observational study monitored 40 elderly patients with asymptomatic meningiomas, of whom 14 (35%) demonstrated tumor progression; however, only five patients (12%) became symptomatic [7].

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

In patients who are considered surgical candidates, the goal of therapy is total surgical excision [2••,19–21, Class II]. As with all brain tumors, completeness of surgical resection is determined by early (<72 hours) postoperative contrast enhanced brain imaging using CT or MRI. Mirimanoff *et al.* [20, Class II] reported recurrence-free survival rates, after total resection, of 93% at 5 years, 80% at 10 years, and 68% at 15 years. Compared with partial resection, recurrence-free survival rates dropped to 63%, 45%, and 9%, respectively. Jaaskelainen [21, Class II], in a study of patients with

benign intracranial mengiomas, found that after complete resection, recurrence rates were 19% at 20-year follow-up. The same group reported that in patients with atypical or malignant meningiomas after complete resection, the risk of recurrence was 38% and 78% at 5 years, respectively.

Radiation therapy should be considered the standard adjunct therapy after partial resection of a meningioma [8••, Class II]. Goldsmith *et al.* [8••], reporting on 140 patients, found an 89% 5-year progression-free survival with adjunct radiotherapy (median dose 54 Gy) in patients with a partially resected benign meningioma. Ten-year progression-free survival was 77%.

The use of SRT in the management of meningiomas continues to evolve [9,10,11•, Class II]. Using LINAC or gamma-knife radiosurgery, SRT has been administered in lieu of external beam radiotherapy for small (<35 mm) tumors that are recurrent or partially resected. In addition, SRT has been used as primary therapy in surgically inaccessible tumors (*ie,* basal meningiomas) or in patients deemed poor surgical candidates, such as the elderly. The studies using SRT to date involve comparatively small numbers of patients (usually <100) and relatively short follow-up times (usually <5 years). Notwithstanding these caveats, results of SRT compare favorably with external beam radiotherapy and surgery in select patients.

Epidemiologic and biochemical evidence (70% of meningiomas are progesterone receptor positive and 30% are estrogen receptor positive) have suggested meningioma growth may be hormone dependent [2••,13, Class III]. As such, a variety of hormonal therapies have been used in the treatment of recurrent benign meningiomas not otherwise treatable by surgery or radiotherapy. The oral progesterone agonist megestrol acetate was used in a small trial of nine patients with no observed response [15]. Subsequently, in a trial of 14 patients, the progesterone antagonist mifepristone was used [16•]. Five objective minor responses were seen, though availability of mifepristone has limited further study. The Southwest Oncology Group reported on a phase 2 trial of oral tamoxifen, an estrogen receptor antagonist, in 21 patients [12, Class II]. One patient achieved a partial response, two patients had a minor response, and six patients had stable disease for more than 6 months.

Recombinant interferon-alpha has been found to inhibit the growth of cultured human meningioma cell lines in vitro [17,18•, Class III]. Three small reports, two in abstract form, have been published. 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 more than 6 months. Schrell *et al.* [13•, Class III] demonstrated in vitro that hydroxyurea, an oral chemotherapy with a variety of antitumoral effects, was a potent inhibitor of cultured meningioma cells by inducing apoptosis. A subsequent clinical trial by Schrell *et al.* [13•, Class III] involving four patients, another by Newton *et al.* [26, Class III] involving 40 patients, and a third trial reported by Mason *et al.* [14, Class III] involving 20 patients suggested in vivo efficacy (>80% with stable disease for a median of 20 to 30 months; Table 5). Currently, a larger Southwest Oncology Group phase 2 trial (SWOG 9811) studying the effect of hydroxyurea for progressive/recurrent intracranial meningioma is underway.

Multidrug chemotherapy trials for recurrent meningiomas, whether aggressive, malignant, or refractory, to surgery and radiotherapy are scant [12,27, Class III]. The best-documented chemotherapy regimen (cyclophosphamide, adriamycin, and vincristine) has been used primarily in an adjuvant setting for the treatment of malignant meningiomas and without a control group; however, response to treatment is difficult to assess [27]. Other published regimens do not report response rates, length of response, or toxicity data, and therefore should be regarded as investigational [12, Class III].

Treatment

Diet and lifestyle

- There are no data to suggest that diet or lifestyle predispose to the development of or are useful in the treatment of meningioma.

Pharmacologic treatment

- Limited data exist regarding the role of hormonal or chemotherapy; however, patients failing surgery and radiotherapy are often considered candidates.
- Several hormonal therapies have been investigated, and the most compelling data exist for mifepristone; however, this agent remains investigational [16•].
- Two immunochemotherapy drugs (interferon-alpha and hydroxyurea) have been used with modest success [12,13•,14,17,18•,26]. Of the two, more data exist for hydroxyurea, and this, in general, would be the first drug used.

Table 4. Computed tomography findings in patients with meningiomas

Tumor location	Benign meningiomas		Malignant meningiomas	
	Patients, *n*	Patients, %	Patients, *n*	Patients, %
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	27	0	0
Fringing	2	1	2	14
Mushrooming	0	0	8	57

Table 5. Hydroxyurea for recurrent meningiomas

Study	Patients, *n* (benign)	Prior radiotherapy	Toxicity (>grade 3)	Response	
				Best response	Median time to penetration
Newton *et al.* [26]	17 (13)	7	28% (15%)	Standard deviation (88%)	20 minutes
Mason *et al.* [14]	20 (16)	8	15%	Standard deviation (50%)	30 minutes

- The treatment of aggressive and malignant meningiomas remains problematic, because recurrence is common (notwithstanding application of surgery and radiotherapy). Chemotherapy for such patients may be prescribed; however, very few data are available to guide therapy [12,27].

Hydroxyurea

Standard dosage	500 mg orally twice daily.
Contraindications	Impaired bone marrow reserve.
Main drug interactions	None.
Main side effects	Myelosuppression.
Special points	This is an oral agent that is easily administered with a low toxicity profile and that is given daily, with neuroradiographic evaluations every 3 months.
Cost/cost effectiveness	Cost is $228 average wholesale (AWS) price for a 3-month treatment.

Interferon-alpha

Standard dosage	1 to 4 million IU/m^2 subcutaneously three times per week.
Contraindications	Impaired bone marrow reserve.
Main drug interactions	None.
Main side effects	Fatigue, flu-like syndrome, and myelosuppression.
Special points	This is an agent with a moderate toxicity profile that is subcutaneously administered, and that is given three times per week, with neuroradiographic evaluations every 3 months
Cost/cost effectiveness	Cost is $3484 AWS price for a 3-month treatment.

Cyclophosphamide, adriamycin, and vincristine

Standard dosage	Days 1 through 3: cyclophosphamide at 500 mg/m^2 intravenously per month. Days 1 through 3: adriamycin at 15 mg/m^2 intravenously per month. Day 1: vincristine at 1.4 mg/m^2 intravenously per month (capped at 2 mg).
Contraindications	Impaired bone marrow reserve.
Main drug interactions	None.
Main side effects	Myelosupression, nausea and vomiting, hemorrhagic cystitis, and cardiotoxicity.
Special points	This is an intravenous regimen with moderate toxicity that is given monthly, with neuroradiographic evaluations every 2 months. Transfusion is often necessary because of myelosupression. Regimen is usually reserved for aggressive and malignant meningiomas.
Cost/cost effectiveness	Cost is $1038 AWS price for a 2-month treatment.

Dacarbazine and adriamycin

Standard dosage	Days 1 through 4: dacarbazine at 900 mg/m^2 per day continuous intravenous infusion every month. Days 1 through 4: adriamycin at 90 mg/m^2 per day continuous intravenous infusion every month.
Contraindications	Impaired bone marrow reserve.
Main drug interactions	None.
Main side effects	Myelosupression, nausea and vomiting, and cardiotoxicity.
Special points	This is an intravenous regimen with moderate toxicity that is given monthly, with neuroradiographic evaluations every 2 months. Transfusion of blood products is often necessary because of myelosupression. Regimen is usually reserved for aggressive and malignant meningiomas.
Cost/cost effectiveness	Cost is $8400 AWS price for a 2-month treatment.

Ifosfamide/mesna

Standard dosage	Days 1 through 5: ifosfamide 2000 mg/m^2 per day continuous intravenous infusion every month. Days 1 through 5: mesna 1200 mg/m^2 per day continuous intravenous infusion every month.
Contraindications	Impaired bone marrow reserve.
Main drug interactions	None.
Main side effects	Myelosupression, nausea and vomiting, and hemorrhagic cystitis.
Special points	An intravenous regimen with moderate toxicity that is given monthly, with neuroradiographic evaluations every 2 months. Transfusion of blood products is often necessary because of myelosupression. Regimen is usually reserved for aggressive and malignant meningiomas.
Cost/cost effectiveness	Cost is $8660 AWS price for a 2-month treatment.

Interventional procedures

Brain imaging—computed tomography or magnetic resonance imaging

Standard procedure	Brain imaging via contrast-enhanced CT or MRI.
Contraindications	Iodine allergy; paramagnetic metals in situ.
Complications	Contrast allergy.
Special points	Brain imaging using CT or MRI is the method of choice for radiographically observing meningiomas and to determine response to therapy [2••].
Cost/cost effectiveness	No data available.

Brain imaging—positron emission tomography or single photon emission tomography

Standard procedure These imaging procedures are used to evaluate metabolic activity as opposed to anatomic data obtained with CT or MRI. Metabolic activity assessment may be useful in determining whether disease progression seen by CT or MRI may represent radiation necrosis rather than tumor recurrence in patients with tumors previously irradiated [2••].

Contraindications None.

Complications None.

Special points Brain imaging using CT or MRI is the method of choice for radiographically observing meningiomas and to determine response to therapy. In selected patients, the differentiation between tumor recurrence and radiation necrosis is difficult. Positron emission tomography or single photon emission tomography may be useful in this situation.

Cost/cost effectiveness Positron emission tomography costs approximately $1800; single photon emission tomography costs approximately $1000 (though varies by institution).

External beam radiotherapy

Standard procedure External beam radiotherapy is used in patients with subtotally resected or recurrent meningiomas; also applied after initial resective surgery in patients with aggressive or malignant meningiomas [2••,8••].

Contraindications Prior cranial irradiation.

Complications Alopecia, nausea, fatigue, or scalp dermatitis is common during and immediately after radiotherapy. Delayed toxicity may involve radiation necrosis, small-vessel arteriopathy, progressive intellectual decline, a Parkinsonian syndrome, and induction of a second cancer.

Cost/cost effectiveness No data available.

Stereotactic radiotherapy

Standard procedure Stereotactic radiotherapy is used in patients with subtotally resected or recurrent meningiomas; also applied to patients with surgically inaccessible tumors or in patients deemed not to be good surgical candidates. SRT may also be administered to patients as a radiotherapy boost after external beam radiotherapy [9,10,11•].

Contraindications Prior SRT.

Complications Delayed toxicity may involve radiation necrosis, small-vessel arteriopathy, or appearance of a cranial neuropathy.

Cost/cost effectiveness No data available.

Surgery

Craniotomy with tumor resection

Standard procedure Craniotomy (discussed in [2••,20,21]).

Contraindications Bleeding disorder; limited expected survival.

Complications Hemorrhage, infection, stroke, and death.

Special points Craniotomy is the only therapy capable of achieving a complete cure, although not all patients are necessarily candidates for resective surgery.

Cost/cost effectiveness No data available.

Assistive devices

Wheelchair, walkers, canes

Usage Some patients before treatment or after treatment have impaired walking and require ambulatory aids. The type of aid is based on the degree of motor impairment.

Special points Need is best assessed by physical therapy.

Cost/cost effectiveness No data available.

Physical/speech therapy and exercise

- Therapy may be beneficial in patients after surgery with speech or motor impairments.
- In patients who are good candidates for rehabilitation, a program of physical or speech therapy may permit a patient to return to work or resume independence in activities of daily living.
- After surgery, some patients may be permanently impaired as a consequence of injury to eloquent regions of brain and therefore may not respond to rehabilitation efforts. However, all patients should be given the opportunity for rehabilitation, because predicting ultimate neurologic outcome is difficult.

Emerging therapies

- Gene therapy using viral vectors.
- Biodegradable wafers containing biologic response modifiers or chemotherapeutic agents.
- Monoclonal antibodies and small molecular inhibitors targeted to meningioma cell surface tumor markers.
- Antiprogesterone agents, such as mifepristone [16•].

Pediatric considerations

- Meningiomas are rare in the pediatric population (2% of all meningiomas and 3% of all pediatric brain tumors) [19].
- Children with meningiomas often have neurofibromatosis type-2 or a history of external beam radiotherapy for tinea capitis.
- Boys are affected as often as girls.
- Tumor location and histology are similar to adults.
- Survival rates are excellent and recurrence rates are low.
- Treatment strategies are similar to adults, with gross total resection the ultimate goal.

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