Role of radiation therapy in treating intracranial meningiomas*

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✓Surgery is the mainstay for many patients with meningiomas, and it remains the standard. In large single-institution series, gross-total resection has been reported to achieve 5-, 10-, and 15-year recurrence-free survival rates of approximately 90, 80, and 70%, respectively. There are a growing number of series of patients with prolonged follow-up in which authors have evaluated fractionated external-beam radiation therapy (EBRT) either as an adjuvant to surgery for subtotally resected, recurrent, or higher-grade meningiomas, or as an alternative to surgery. The primary focus of this review is EBRT, but to lend perspective, a comparative analysis of surgery and radiosurgery is also provided. (DOI: 10.3171/FOC-07/10/E4)

KEY WORDS • brain neoplasm • meningioma • radiation therapy • radiosurgery

CUSHING coined the term “meningioma”²⁶ to describe tumors that principally originate from the meningeal coverings of the brain and spinal cord. Considerable progress has been made characterizing histological grades, defining aggressive variants, and modernizing approaches to treatment, but many crucial questions remain. In part, this is because meningiomas tend to progress slowly and thus require long-term vigilance, which reveals that considerable morbidity, and even death can be caused by this neoplasm.^{22,43}

Epidemiology

Meningiomas are now the most frequently reported primary intracranial neoplasm,²² constituting approximately 30% of primary central nervous system tumors.^{16,17,22,67,68} Many are identified solely on the basis of imaging findings; in recent studies, 35 to 62% were diagnosed on the basis of imaging alone.^{31,35} Furthermore, meningiomas have been identified in 2.3% of all autopsy reports.⁹¹ Therefore, it is likely that more intensive use of imaging will increase the detection of meningiomas.

The risk of a patient developing a meningioma increases with age.^{1,22,85,133} Meningiomas have rarely been reported during fetal development and infancy.^{7,34,97,100,157} Except in the setting of NF2,¹⁰⁰ however, they are infrequent in the pediatric population.^{80,100} More aggressive clinical and histological features have been noted in children and young adults.⁹⁹ In terms of the absolute numbers of meningiomas, the peak incidence occurs during the sixth and seventh decades of life.¹⁰² However, the age-specific rate of development of meningiomas continues to rise thereafter. Figure 1, created based on data from a large epidemiological study published in 2005, highlights that the age-specific incidence continues to rise even for individuals older than 85 years.²²

Meningiomas occur more frequently in females, with a female/male ratio of approximately 2:1.^{41,74,80,85,133,150} Progesterone and estrogen receptors have been identified in greater than 70 and 30% of meningiomas, respectively.^{102,149} Increased estrogenicity is associated with an increase in tumor-related symptoms during pregnancy or the luteal phase of menses.^{30,149} An increased risk of breast cancer has been described in patients with meningioma, as has an

Abbreviations used in this paper: EBRT = external-beam radiation therapy; GTR = gross-total resection; MR = magnetic resonance; NF2 = neurofibromatosis Type 2; ONSM = optic nerve sheath meningioma; PFS = progression-free survival; SRS = stereotactic radiosurgery; STR = subtotal resection; WHO = World Health Organization.

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FIG. 1. Bar graph demonstrating the age-specific incidence of meningioma, based on data from the Central Brain Tumor Registry of the United States. The graph was derived using data from the article by Claus et al.

increased relative risk of meningiomas with breast cancer.¹⁴⁹ However, androgen receptors have been identified in nearly 40% of meningiomas,¹⁰² and therapies designed to exploit hormone receptor overexpression have, to date, met with disappointing results.^{98,112}

Origin of Meningiomas

The origin of the majority of meningiomas is unknown.²² Associations have been made with hormones, growth factors, NF2, ionizing radiation, and trauma.^{5,10,30,36,39,48,51,80,99,100,102,118,119,139} Nearly all NF2-associated meningiomas have mutations of the NF2 gene on 22q12.¹¹⁵ Most families identified as susceptible to meningiomas have alterations of the NF2 locus on chromosome 22.^{75,115} Monosomy of chromosome 22 is the most common cytogenetic alteration in meningiomas.

Histopathology

Cell of Origin

Meningiomas are believed to arise from arachnoid cap cells (the epithelioid cells on the outer surface of arachnoid villi), or meningotheial progenitor cells.^{23,121} Meningiomas are cytologically similar to cells within arachnoid caps; arachnoid villi are identified in greater numbers at sites where meningiomas frequently arise; and cap cell clusters appear to increase with age, paralleling the age-related occurrence of meningiomas.⁹⁷

Tumor Grade

The WHO published its grading criteria in 2000.⁷⁶ An update is expected this year (2007). The 2000 and 2007 criteria are expected to be similar; brain invasive meningiomas are now regarded as Grade II, even in the absence of atypia or anaplasia.¹⁰² As depicted in Fig. 2, using these criteria, stronger associations between grade and outcome have been demonstrated in large series.^{46,65,103,104}

Benign meningiomas (WHO Grade I) constitute approx-

FIG. 2. Kaplan-Meier estimated recurrence-free survival (RFS) by WHO tumor grade from a compiled series of 643 patients from studies by Perry et al., 1997 and 1999. The number of patients with each grade is given, as is the percentage of patients with each grade. The grading criteria used in this study have been incorporated into the current WHO grading scheme. Courtesy of Christine Lohse, Biostatistics Division, Mayo Clinic, and reprinted with permission from Springer.

imately 70 to 85% of intracranial meningiomas. With appropriate treatment, more than 80% of WHO Grade I meningiomas remain progression-free at 10 or more years.^{24,94,103,104} Atypical meningiomas (WHO Grade II) likely account for 15 to 25% of intracranial meningiomas.^{103,104,153} Authors of single-institution series have tended to include a smaller percentage of patients with Grade II tumors, ranging from 4.7 to 9.6%.^{54,82} It is important to recognize Grade II meningiomas, given that they carry a seven- to eightfold increased recurrence risk at 3 to 5 years.⁹⁸ Only approximately 40 to 60% of patients with Grade II meningiomas remain disease-free at 10 years.^{24,48,54,103,104} One to four percent of intracranial menin-

FIG. 3. Cumulative proportion of patients free of recurrence against the number of years since surgery. Reprinted with permission from Adegbite et al., *J Neurosurg* 58:51-56, 1983.

TABLE 1

*Extent of resection according to Simpson grading**

Resection Grade	Definition	Recurrence (%)
1	GTR of tumor, dural attachments, & abnormal bone	9
2	GTR of tumor, coagulation of dural attachments	19
3	GTR of tumor w/o resection or coagulation of dural attachments or extradural extensions (invaded or hyperostotic bone)	29
4	partial resection of tumor	44
5	simple decompression (biopsy)	—

* — = not applicable.

giomas are anaplastic (WHO Grade III).^{54,103,104,153} They have a median recurrence-free survival of fewer than 2 years.^{103,104} We plan no specific review of Grade III meningiomas.

Treatment and Outcome

Authors of many studies have highlighted excellent local control after resection, radiosurgery, and fractionated EBRT at approximately 5 years, but this cannot be considered definitive. Adegbite and coworkers¹ documented that even with thorough resection, the likelihood of recurrence is high with a sufficient observation interval of 15–20 years (Fig. 3). A few other series, also with long-term follow-up, have shown that gross totally resected meningiomas recur 20–30% of the time at 10 to 15 years.^{24,85,133}

Surgical Resection

The completeness of surgical removal is an important prognostic feature.^{24,29,108,133} Resection of the meningioma, its involved dura, and any involved soft tissue and bone is an accepted procedure,³⁰ and achieves high rates of local control. The extent of resection was classically defined by Simpson,¹²⁸ who linked it to recurrence risk, summarized in Table 1. Kinjo and colleagues⁶¹ defined a more extensive resection as “grade zero,” entailing gross-total resection of the primary, any hyperostotic bone, and all involved dura with a 2 cm dural margin. They observed no local recur-

TABLE 2

*Sites of meningioma in 581 patients**

Site	% of Patients
parasagittal falx	18.6
convexity	16.8
multiple sites†	16.3
sphenoid wing	15.3
posterior fossa	13.6
parasellar area	10.5
anterior visual pathway	2.5
clivus	2.4
foramen magnum	2.4
intraventricular area	1.0

* Due to the requirements of rounding, adding the percentages amounts to 99.4%.

† The item “multiple sites” refers principally to meningiomas which occupy more than one area. Only 3% of patients had multiple lesions. Reprinted with permission from Stafford et al., *Mayo Clinic Proceedings* 73:936–942, 1998.

TABLE 3

Relative frequency of complete excision in 225 patients

Meningioma Location	No. of Patients	% Complete Excision
convexity	47	96
orbit	5	80
spine	18	78
olfactory groove	22	77
parasagittal area/falx	38	76
parasellar region	28	57
posterior fossa	31	32
sphenoid ridge	36	28
total	225	64

rences, with more than half of 37 patients followed over 5 years.⁶¹

Table 2 reviews the distribution of intracranial meningiomas. The likelihood of gross-total resection varies considerably by primary sites.^{29,41,85,108} Table 3 reviews the likelihood of complete excision. Overall, at least one third of meningiomas reported in surgical series are not fully resected.^{85,108}

Gross-Total Resection Alone. Gross-total resection for benign meningiomas is considered definitive.^{24,85,108,133} Three large series with extended follow-up are listed in Table 4. Remarkably similar local recurrence rates were reported in all: 7 to 12%, 20 to 25%, and 24 to 32% at 5, 10, and 15 years, respectively. Typically, GTR connotes Simpson Grades 1 and 2,¹⁰⁸ and sometimes Grade 3 resection.²⁴ Authors of a study conducted at the University of Florida found no significant difference in local control or cause-specific survival between Simpson Grade 1 to 3 resections.²⁴

Subtotal Resection Alone. Subtotal resection alone remains common in practice, and Table 5 summarizes outcomes following STR alone, from four series of patients with 10 to 20 years of follow-up; the 5-, 10-, and longer than 15-year progression rates following subtotal resection were 37 to 47%, 55 to 63%, and greater than 70%, respectively.^{24,85,133,151}

Radiation Therapy

Radiation therapy improves local control. Factors considered in the decision to use radiotherapy include the extent of resection,^{24,85,128,133} grade,^{103,104} and histological subtype.⁷⁶ Secondly, one might also consider imaging findings such as edema and calcifications,^{49,80,89} age,^{55,99} and perhaps menopausal status,⁵⁵ although these remain less well defined.

TABLE 4

Three large single-institution series with 10 to 15 years' follow-up, documenting rates of recurrence following GTR alone

Authors & Year	No. of Patients	Local Recurrence Rate (%)		
		5-yr	10-yr	15-yr
Mirimanoff et al., 1985	145	7	20	32
Condra et al., 1997	175	7	20	24
Stafford et al., 1998	465	12	25	—

TABLE 5

Four single-institution series with 10- to 20-year follow-up, assessing rates of recurrence following STR alone

Authors & Year	No. of Patients	Local Progression Rate (%)			
		5-yr	10-yr	15-yr	20-yr
Wara et al., 1975	58	47	62	—	74
Mirimanoff et al., 1985	80	37	55	91	—
Condra et al., 1997	55	47	60	70	—
Stafford et al., 1998	116	39	61	—	—

Data pertaining to a total of 42 studies with 4585 patients treated with radiotherapy or radiosurgery are summarized in Tables 6 and 7. These data substantiate that irradiation is beneficial as an adjunct to surgery following subtotal resection, as treatment for recurrent meningiomas, or as primary therapy. For comparative purposes, a brief consideration of radiosurgery for meningiomas follows.

Stereotactic Radiosurgery

Local control rates following SRS are 75 to 100% at 5 to 10 years.^{45,62,64,71,91,108,117,123,134,147} Outcomes from several radiosurgery series are summarized in Table 6. Stereotactic radiosurgery is generally considered most appropriate for meningiomas less than 3 to 4 cm in diameter, with distinct margins, and with sufficient distance from critical healthy tissues to allow for appropriate normal tissue dose restrictions as well as adequate target dose. DiBiase and coauthors³¹ reported 5-year disease-free survival rates of 91.9% for patients with meningiomas 10 cm³ or smaller (equivalent diameter 2.7 cm) versus 68% for larger tumors. Au-

thors of many series have used margin doses in the 10- to 18-Gy range. Ganz and associates³⁷ noted that a minimum peripheral tumor dose of 10 Gy or less was associated with a higher risk of failure, whereas at least 12 Gy resulted in improved local control. Morita and colleagues⁸⁶ subsequently recommended tumor margin doses of at least 15 to 16 Gy. Stafford and coauthors¹³⁴ reported no improvement in 5-year local control with doses of at least 16 Gy. Kondziolka and associates⁶² reported no improvement with marginal doses of at least 15 Gy. Margin doses ranging from 12 to 16 Gy are now widely used.^{35,64,70,93,116,132}

Early reports of SRS were associated with a high complication rate. For example, in 41 patients with a median follow-up of 3.5 years, Kondziolka and colleagues⁶² noted worse outcomes in cases of larger tumors, prior surgery, or with pre-SRS neurological deficits. The adverse events most frequently attributed to SRS are cranial nerve deficits and peritumoral edema. Serious, but uncommon side effects include radiation necrosis,^{33,47,62} peritumoral cyst formation,¹³⁴ carotid artery stenosis,¹³⁵ and hypothalamic dysfunction.⁴⁵ With margin doses of 14 to 16 Gy, authors of some studies have identified new or worsened cranial nerve deficits in approximately 8% of patients.^{31,64,134,136,140,142} Neuropathies are encountered more frequently with the optic, cochlear, and trigeminal nerves. Motor nerves tend to tolerate radiosurgery comparatively well. Roche and colleagues¹¹⁷ observed no new oculomotor deficits in 80 patients with cavernous sinus meningiomas with a mean maximum prescription dose of 28 Gy and a median follow-up of 30.5 months. Conversely, sensory nerves of the anterior visual pathway have been particularly susceptible. Doses of only 10 Gy or less^{86,136} carry a roughly 1 or 2% rate of optic neuropathy. With higher doses, the rate and severity of complications rise steeply.^{69,136}

TABLE 6

*Compiled stereotactic radiosurgery with reported 5-year PFS rates**

Authors & Year	No. of Patients	FU (mos)†	No Histology (%)‡	Dose (Gy)	≥ 5-yr PFS§
Chang et al., 1997	55	48	—	18	98
Chang et al., 1998	24	46	—	17.7	100
Hakim et al., 1998	127	31	54	15	89
Kondziolka et al., 1999	99	43	16	93	
Liscak et al., 1999	53	19	64	12	100
Morita et al., 1999	88	35	44	16	95
Roche et al., 2000	80	31	63	14	93
Shin et al., 2001	15	42	30	10–12	75 (5- & 10-yr PFS)
	22		30	14–18	100 (5- & 10-yr PFS)
Stafford et al., 2001	168		41	16	93
Lee et al., 2002	159	35	52	13	93 (97 if SRS sole tx)
Nicolato et al., 2002	111	48	50	15	96
Spiegelmann et al., 2002	42	36	—	14	97.5
Flickinger et al., 2003	219	29	100	14	93 (5- & 10-yr PFS)
Iwai et al., 2003	42	49	48	11	92
Pollock et al., 2003	62	64	46	17.7	95 (7-yr PFS)
Roche et al., 2003	32	56	75	13	100
Chuang et al., 2004	43	75	48	16	90 (7-yr PFS) (100 if SRS sole tx)
DiBiase et al., 2004	137	54	62	14	86.2 (91.9 if < 10 cm ³)
Zachenhofer et al., 2006	36	103	31	16.8	94 (at 5 & 8 yrs)

* Patients in these reports typically, but not exclusively, had either known or presumed low-grade meningiomas. Abbreviations: FU = follow-up; tx = treatment.

† Stated as the mean or median value.

‡ This column refers to the percentage of patients diagnosed with meningioma on the basis of neuroimaging findings.

§ Actuarial intervals other than 5 years are given in parentheses.

TABLE 7
Compiled series allowing for comparison in the rates of PFS for
patients treated with GTR, STR, or with STR plus EBRT *

Authors & Year	No. of Patients	FU (mos)	5-yr PFS (%)		
			GTR	STR	STR & EBRT†
Adegbite et al., 1983	114	10–276	90	45	82
Mirimanoff et al., 1985	225	>60 (65%)	93	63	
Barbaro et al., 1987	135	78	96	60	80
Taylor et al., 1988	132	>60 (60%)	96	43	85
Glaholm et al., 1990	117	80			84
Miralbell et al., 1992	115	57		48	88 (8-yr PFS)
Goldsmith et al., 1994	117	40			89 (98 after 1980)
Mahmood et al., 1994	254	61	98	54	
Peele et al., 1996	86	46		52	100
Condra et al., 1997	246	98	95	53	86
Stafford et al., 1998	581	55	88	61	
Maguire et al., 1999	28	41			92 (4-yr PFS)
Nutting et al., 1999	82	108			92
Vendrey et al., 1999	156	40			89
Wenkel et al., 2000	46	53			100
Debus et al., 2001	189	35			98 (FSRT)
Dufour et al., 2001	31	73			93 (10-yr PFS)
Pourel et al., 2001	26	30			95
Uy et al., 2002	40	30			93
Pirzkall et al., 2003	20	36			100
Selch et al., 2004	45	36			98 (3-yr PFS)
Soyuer et al., 2004	92	92	77	38	91
Milker-Zabel et al., 2007	94	53			93.6 (Grade I 96.3)

* Patients in these reports typically, but not exclusively, had either known or presumed low grade meningiomas. Abbreviation: FSRT = fractionated stereotactic radiosurgery.

† Actuarial intervals other than 5-years are given in parentheses.

Posttreatment edema has been widely reported subsequent to SRS (Table 8).^{38,59,62,90,113,147} Meningiomas produce vasoactive mediators.^{56,80,95,111} Edema is more commonly encountered with nonbasal primary tumors, which are apt to have a broader pial interface^{6,49} permitting vasogenic substrates greater access to adjacent brain. Basal primaries have more limited pial involvement.^{6,49,50} Edema developed in 25 to 78% of the patients with nonbasal meningioma, compared with 0 to 22% of patients with basal primary tumors. With parasagittal meningiomas, for which edema has been frequently reported,⁶² bridging vein and/or sagittal sinus occlusion may also contribute. Other factors potentially associated with an increased risk of edema are the following: margin dose greater than 15 Gy, tumor size (diameter ≥ 3 cm or volume ≥ 4 cm³), and the presence of pretreatment edema.

External-Beam Radiation Therapy

Meningiomas were historically considered resistant to irradiation,^{60,85} and authors of several older retrospective studies described infrequent radiographic regression.^{1,60,148,155} In addition, there has been apprehension regarding the malignant degeneration of irradiated tumors as well as about the relationship between irradiation and the ultimate development of meningiomas.^{40,118,119,139} Therefore, many patients with inoperable or subtotally resected meningiomas have been observed.^{3,55,133} Malignant degeneration now is widely believed to be related to the natural history of a subgroup of meningiomas, and has never been explicitly linked with radiation therapy. The risk of developing a

meningioma after cranial irradiation has been reviewed by Stojan et al.,¹³⁹ who reported the actuarial risk after radiation therapy to be 0.53% at 5 years, and 8.18% at 25 years.

In the 1970s and early 1980s, several authors reached the conclusion that EBRT improved local control after incomplete resection or recurrence,^{11,15,18,151} despite the fact that meningiomas often remained stable or regressed slowly.

Primary EBRT. Radiation therapy may be used as primary treatment following biopsy, or even on the basis of imaging findings.^{15,24,77,106,122} An early report described 47% disease-free survival at 15 years in 32 patients who underwent EBRT without resection. This was lower than the 61% rate following partial resection plus radiotherapy.⁴⁰ In a more recent series, Debus et al.²⁸ noted no difference in outcomes between patients who underwent primary EBRT (59 patients) and those who underwent surgery plus EBRT (130 patients). In fact, there were no recurrences in patients treated with radiotherapy alone; the 10-year recurrence-free probabilities were 100%.²⁸ Several other authors have also reported excellent results with primary EBRT.^{15,24,77,92,106,122}

Primary EBRT for ONSM. Optic nerve sheath meningiomas arise from the dura encompassing the optic nerve, and account for only 1 to 2% of meningiomas.^{13,72,73,81,129} Surgery plays a very limited role in the management of ONSMs. Observation results in gradual loss of vision, and surgery is often associated with immediate blindness of the affected eye. Resection of ONSMs while keeping the optic nerve in situ has been tried, but carries a high risk of visu-

TABLE 8
Six series (with 226 total patients) with new or worsening edema following SRS*

Authors & Year	No. of Patients	FU (yrs)	Dose in Gy (range)	Edema in % (basal vs nonbasal)†	Comment
Ganz et al., 1996	34	1–3	15 (12–25)	21 (7 vs 71%)	86% of patients with edema: margin dose >18 Gy; 12 Gy adequate for LC
Nakamura et al., 1996	48	1	15 (mean)	8 (0 vs 25%)	edema with 15–24 Gy; 25% resolved
Kondziolka et al., 1998	203	3.5	15 (9–32)	10 (all parasagittal)	3- & 5-yr actuarial edema 16%; more common if >3 cm occurred 1–23 mos after SRS; all resolved (median 15 mos)
Vermeulen et al., 1999	95	2.3	17 (8–20)	32 (22 vs 41%)	1% basal vs 4% non-basal had “deteriorating” edema w/o tumor growth
Ramsey et al., 2002	23	1.4	14 (9–18)	39 (22 vs 78%)	factors for edema: volume >4 cm ³ (p = 0.005) parasagittal (p = 0.006); pre-SRS edema (0.06)
Kim et al., 2005	26	2.7	16 (12–20)	43 (all nonbasal)	mean edema more likely if >4.2 cm ³ (p = 0.02); duration of symptoms 9 months

* LC = local control.

† The methods of assessing edema varied from clinical (Kondziolka) to imaging (Ganz & Vermeulen) to a combination of both (Nakamura, Ramsey, and Kim).

al complications and local recurrence.^{8,25,52,58,143} Resection commonly impairs the blood supply and results in blindness, even though the nerve is left grossly intact.

External-beam radiation has become integral in the management of ONSMs.^{92,130,143} Turbin et al.¹⁴³ reported on 64 patients with ONSM and found that radiation therapy alone provided more favorable outcomes than observation, surgery alone, or even surgery plus EBRT. They used total doses ranging from 40 to 55 Gy, and had median follow-up periods of 8.3 years. In another study, and after a median follow-up of 51.3 months, Narayan et al.⁹² found no radiographic progression in any of their 14 patients with ONSMs treated with conformal EBRT, and 86% had either improved or stable visual acuity. This study, along with six additional studies in which highly conformal or fractionated stereotactic therapy was used, in composite analyzing of 75 eyes, has reached similar conclusions.^{9,12,72,92,107,114,120} Overall disease control is excellent (95%); early visual improvement (within 3 months of radiotherapy) is often attained (54.7%); and complications are relatively uncommon. With these findings, it has been suggested that earlier treatment of symptomatic patients may provide better visual outcome;¹³ however, there is no uniform agreement as to whether patients with both stable ONSMs and stable vision should be approached with observation or early EBRT.

Postoperative EBRT. Many retrospective studies now support a role for postoperative EBRT after STR. These have shown improvement in local control (Table 7), and possibly even survival.^{24,79}

Technical Factors and Dose–Volume Considerations. With image-based techniques, treatment can be delivered with more precision and conformality (Fig. 4), and improved results are to be expected.^{88,122,126} Improvements in local control have, in fact, been documented with computed tomography- or MR imaging-based planning. Goldsmith et al.⁴³ and Milosevic and colleagues⁸³ each substantiated improvements in local control consequent to improved targeting with modern imaging.⁴¹ Patients whose treatments were planned and delivered in this fashion had a remarkable 10-year PFS rate of 98% compared with 77% without.⁴³

Recommended doses generally range from 50 to 55 Gy

in fractions of 1.8 to 2.0 Gy.^{15,24,41,42,66,92,125,144,150} Goldsmith et al.⁴³ reported that doses greater than 52 Gy resulted in an improved 10-year local control of 93% compared with 65% with lower doses, but this finding lost significance on multivariate analysis. Among 67 patients, Winkler et al.¹⁵⁴ found no clear dose response from 36 to 79.5 Gy.

The recommended planning target volume has ranged from gross tumor volume (that is, the tumor visible on MR imaging) or the gross tumor volume plus a margin, ranging from a few millimeters to up to 4 cm.^{8,24,28,40,82,127} Marginal failures are uncommon.^{28,93} The targeting of the “dural tail” remains contentious. Figure 5 depicts a dural tail, not included within the defined target.³¹ Pathology studies have revealed the dural tail to be composed entirely or almost entirely of hypervascular dura in most cases,^{2,14,57,87,101} and including it in the radiotherapy field is of questionable value.

Planning target volumes with radiosurgery have tended to include only the contrast-enhancing tumor without a margin.^{63,64,123,134} Nevertheless, as illustrated in Fig. 6, by 1 year the tumor had already modestly responded and the dural tail largely resolved. Nicolato and colleagues⁹³ found no advantage to larger radiosurgery margins. With median follow-up of 4 years, they had 100% tumor growth control with a conformity index (ratio of prescription isodose volume to target volume) of 1.5 or less. Using fractionated radiotherapy with 2-mm margins, Debus et al.²⁸ noted no marginal failures in 189 patients with a 3-year median follow-up period.

Another confounding variable in the definition of the planning target volume is hyperostosis.^{27,105} Pieper et al.¹⁰⁵ correlated imaging to histopathology in 26 patients; tumor invasion of the hyperostotic bone was conclusively present in all but one. In addition, nine of 25 patients without imaging evidence of hyperostosis were found to have histological invasion of bone. It remains unresolved whether resection of bone, or for that matter its inclusion within the radiation therapy target, is necessary for every patient. Recurrence rates for patients who have undergone GTRs not inclusive of hyperostotic bone have traditionally been low, as have recurrences after radiosurgery and EBRT regardless whether neighboring bone was targeted.

FIG. 4. Magnetic resonance image and isodoses for radiation therapy of a paracavernous meningioma, treated to 54 Gy in 30 fractions. The dose was prescribed at the isocenter. The percentage values for each of the pictured isodoses are given in the legend at the lower right-hand corner of the image. Courtesy of Dennis Shrieve, M.D., Chair of Radiation Oncology, Huntsman Cancer Institute, University of Utah.

Toxicity of EBRT. The side effects of EBRT, especially with current methods of treatment planning and delivery, are relatively uncommon, but by no means are they negligible. In the largest recent series of fractionated irradiation in the literature, Debus et al.²⁸ reported on 189 patients treated with a highly conformal stereotactic approach, using median daily fractions of 1.8 Gy to a mean dose of 56.8 Gy. With a median follow-up of nearly 3 years, they identified clinically significant (Grade 3) toxicity in four patients (2.2%), three (1.7%) in the absence of a preexisting deficit. These were reduced vision, a new visual-field deficit, and trigeminal neuropathy. This is, however, a substantial improvement over the 38% reported by Al-Mefty et al.⁴ with older methods of radiation delivery.

Goldsmith et al.⁴³ recognized complications in five (3.6%) of 140 patients, which they believed may have been attributable to EBRT. These were retinopathy in two, optic neuropathy in one, and cerebral necrosis in two patients.⁴³ They also constructed a model to predict optic nerve tolerance, and recommended a maximum dose of 890 optic ret (for example, 54 Gy in 30 fractions).⁴² Optic complications are quite rare with doses lower than 54 Gy, particularly with fractional doses of 2.0 Gy or less.^{40,84,106} Uy et al.¹⁴⁵ noted no optic pathway toxicity with a median dose of 50.4 Gy and fractions of 1.7 to 2 Gy. The beneficial impact of lower doses per fraction on optic tolerance has been recently confirmed by Shrieve and colleagues,¹²⁵ who concurred that 54 Gy (in 30 fractions) was both safe and effective.

FIG. 5. Magnetic resonance image and isodoses for intensity modulated radiation therapy of a cerebellopontine angle meningioma, treated to 54 Gy in 30 fractions (fx) prescribed to the 90% isodose. In this case, the dural tail was not specifically targeted, although it was largely encompassed by the 70% isodose volume. The yellow line is the 70% isodose, green 50%, and sky-blue 30%.

Nonocular cranial nerve deficits may occur²⁸ but are uncommon. Selch and colleagues¹²² found no treatment-related cranial neuropathy in 45 patients with cavernous sinus meningiomas that were treated with fractions of 1.7 to 1.8 Gy to a median dose of 50.4 Gy. Urie and coauthors¹⁴⁴ also remarked that doses in this range rarely cause cranial neuropathy.

Brain or brainstem necrosis is also uncommon but has been observed by Goldsmith et al.⁴² and others.^{4,84} Al-Mefty et al.⁴ reviewed post-EBRT toxicity in 58 adult patients with a variety of skull base, parasellar, or pineal region tumors. Seventeen (29%) developed late brain parenchymal changes, with latencies of 4 months to 23 years. These included encephalomalacia, cerebral atrophy, gliosis, and/or necrosis, generalized or involving the temporal lobes in 14 (82%) of the 17 cases.⁴ Such occurrences are almost certainly related to antiquated treatment techniques, for example, low-energy opposed lateral fields. Integral doses to the temporal lobes and to large volumes of untargeted brain are much lower with current multifield conformal and intensity modulation.

Pituitary dysfunction,^{4,84,94,106} cerebrovascular events,^{40, 94,122} second malignancy,^{4,94} orbital fibrosis,⁷⁷ and other sporadic toxicities have been noted. In an older series in which an array of techniques and doses was used, Glaholm et al.⁴⁰ found that all complications occurred with the convention of treating only a portion of the fields daily, and with fractional doses greater than 1.8 Gy (to final doses of 50–55 Gy).

Edema is uncommon following EBRT. Table 7 summarizes data from 23 EBRT studies with a total of 2971

patients. Only six patients (0.2%) reportedly developed edema, and two of these six were asymptomatic. Selch and colleagues,⁸⁴ who specifically evaluated edema, noted none in 45 patients with 3 years of median follow-up.

Authors of some retrospective studies, typically with less conformal techniques, have identified personality changes,¹⁴⁵ and memory loss^{24,77,84,94} as complications of EBRT. Cognitive outcome was prospectively evaluated by Steinvorth et al.,¹³⁷ with the aid of a comprehensive battery administered before, after the first fraction, at completion, and 12 months subsequent to EBRT. They observed no significant cognitive deterioration.¹³⁷

Treatment of Atypical Meningiomas

Atypical (WHO Grade II) meningiomas comprise roughly 20% of all meningiomas (Fig. 2). Most investigators have recommended irradiation, irrespective of resection extent.^{24,48,154} However, in one study, in which eight of 22 patients with atypical meningiomas received postoperative EBRT, local control was 87% at 5 and 10 years following GTR, and EBRT had no significant impact on local control or overall survival.⁴⁴ That series highlighted some of the difficulties in deciphering the literature respective to atypical tumors. The sample size is small, the percentage of patients with Grade II tumors (6.7%) is too low to be representative of current WHO grading, and the doses used (50–54 Gy) may be too low for Grade II tumors.⁴⁸ Hug and associates⁴⁸ found that the local control of atypical meningiomas was significantly enhanced by cumulative doses of at least 60 cobalt Gy equivalents.⁴⁸ Perry and colleagues¹⁰⁴ reported 108 atypical meningiomas treated with modern surgical techniques, grading, and postoperative imaging and found a 5-year recurrence rate of 40% even after GTR. In another study, recurrences of atypical meningiomas after either subtotal or “radical subtotal resection” were 39 and 61% at 5 and 10 years, respectively.¹³³

Radiosurgery has been used in the treatment of atypical meningiomas. Stafford and colleagues¹³⁴ described 5-year actuarial local control of 93% for Grade I meningiomas, compared with 68% for Grade II meningiomas. This is very similar to the 64% (seven of 11 patients) reported by Condra et al.²⁴ with lower EBRT doses, but inferior to the 5-year local control of 90% with at least 60 cobalt Gy equivalents observed by Hug and coauthors.⁴⁸ There is relative consensus for irradiation following subtotal resection; however, it is difficult at present to predict which patients with Grade II tumors that were gross-totally resected will benefit from adjuvant therapy.

Treatment of Recurrent Meningiomas

Recurrent meningiomas exhibit a several-fold increased rate of progression over newly diagnosed tumors.^{24,84,85,141} Miralbell and coauthors⁸⁴ found a 78% 8-year PFS in patients treated with surgery and EBRT for recurrent tumors, versus 11% with surgery alone.⁸⁴ Similarly, Taylor et al.¹⁴¹ found the respective 5-year PFS rates to be 88% compared with 30%.¹⁴¹ They noted that the 5-year overall survival was 90% with surgery plus EBRT compared with 45% after surgery alone. These data support aggressive treatment for recurrent meningiomas.

FIG. 6. Magnetic resonance images before and after radiosurgery of a large petroclival and cavernous sinus meningioma treated with single fraction radiosurgery, 14 Gy to the 50% isodose. The dural tail was not targeted. A: The long enhancing tails of dura bilaterally around the tentorium are seen. B: The largest pretreatment dimensions of the meningioma are shown. C: Follow-up image obtained 1 year after radiosurgery, demonstrating modest tumor shrinkage and resolution of the majority of the untreated dural tail.

Comparative Outcome: EBRT and SRS

Tables 6 and 7 display data from numerous studies suggesting relative equivalence of EBRT and SRS with regard to PFS, with the caveat that patient selection differs significantly between these two approaches. Table 9 encapsulates these data further and reveals that 5- to 10-year PFS rates have ranged from 80 to 100% with EBRT and from 75 to 100% with SRS. For example, Sibtain and Plowman¹²⁷ published a study comparing EBRT and SRS for cavernous sinus meningiomas. They retrospectively evaluated 13 patients with tumors smaller than 3 cm in diameter, most of whom received radiosurgery, and 15 patients with tumors larger than 3 cm, most of whom had EBRT. Tumors in all patients were locally controlled (follow-up 12–83 months).

Conclusions

As a consequence of a frequently observed pattern of slow growth as well as a lack of large cooperative group or randomized trials, standardized recommendations are difficult to formulate. With these limitations, we make the following suggestions.

Small, asymptomatic, stable, or slowly progressive meningiomas can be carefully observed with clinical evaluations and serial imaging. For other patients, GTR remains the benchmark against which other therapeutic strategies should be measured. However, complete removal within the constraints of acceptable morbidity is often not possible. Indeed, meningiomas of the cavernous sinus or petroclival region often involve critical neural or vascular structures, and are generally unresectable.¹³⁸

Following subtotal resection, radiation therapy improves local control, and in some series, survival.²⁴ However, there are no randomized data to support this observation, and it is still debatable whether these patients should be carefully observed or treated preemptively. This decision is complex, given that some patients will do well for many years after subtotal resection alone.

There is growing experience with radiotherapy (EBRT

or SRS) as a primary treatment modality, either after a limited biopsy or based purely on imaging findings. Fractionated EBRT and radiosurgery result in comparable local control rates, and either can be recommended for many patients, but not for all. External-beam radiation therapy is suitable for a broader range of patients, whereas excellent outcome with SRS is realized among a more selected cohort. Radiosurgery is most judiciously applied to smaller meningiomas located at an adequate distance from the optic apparatus, and perhaps those associated with a low risk for developing edema. Fractionated EBRT does not have these limitations. With currently accepted techniques and dose and fractionation guidelines, EBRT appears to carry only a small risk of side effects such as optic neuropathy or edema.

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TABLE 9

*Compiled series allowing comparison of fractionated EBRT with SRS, with 5- to 10-year PFS as the end point**

Treatment Type†	No. of Patients	FU range in mos (mean or median)	5- to 10-yr PFS (%)
SRS combined	1614	19–75	75–100
EBRT combined	2971	30–108	80–100
SRS recent	883	29–103	90–100
EBRT recent	291	30–92	91–100

* Patients in the above reports typically, but not exclusively, had either known or presumed low-grade meningiomas.

† “Combined” includes the full range of data from Tables 5 and 7. “Recent” refers to those reports published in the last 5 years (i.e., since 2002).

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