JNS

LITERATURE REVIEW

J Neurosurg 122:4–23, 2015

Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review

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Evolving interest in meningioma, the most common primary brain tumor, has refined contemporary management of these tumors. Problematic, however, is the paucity of prospective clinical trials that provide an evidence-based algorithm for managing meningioma. This review summarizes the published literature regarding the treatment of newly diagnosed and recurrent meningioma, with an emphasis on outcomes stratified by WHO tumor grade. Specifically, this review focuses on patient outcomes following treatment (either adjuvant or at recurrence) with surgery or radiation therapy inclusive of radiosurgery and fractionated radiation therapy. Phase II trials for patients with meningioma have recently completed accrual within the Radiation Therapy Oncology Group and the European Organisation for Research and Treatment of Cancer consortia, and Phase III studies are being developed. However, at present, there are no completed prospective, randomized trials assessing the role of either surgery or radiation therapy. Successful completion of future studies will require a multidisciplinary effort, dissemination of the current knowledge base, improved implementation of WHO grading criteria, standardization of response criteria and other outcome end points, and concerted efforts to address weaknesses in present treatment paradigms, particularly for patients with progressive or recurrent low-grade meningioma or with high-grade meningioma. In parallel efforts, Response Assessment in Neuro-Oncology (RANO) subcommittees are developing a paper on systemic therapies for meningioma and a separate article proposing standardized end point and response criteria for meningioma.

http://thejns.org/doi/abs/10.3171/2014.7.JNS131644

KEY WORDS meningioma; outcomes; surgery; radiotherapy; oncology

Harvey Cushing first used the term "meningioma" in a 1922 publication describing tumors that originate from the meningeal (dural) coverings of the brain and spinal cord.[19] Since then, considerable progress has been made, including improved methods of treatment, better characterization of histology with the development of grading systems that provide more accurate prognostic information, use of proliferative markers such as MIB-1, and gains in translational research that have improved the understanding of the molecular genetics of these tumors.

With reference to molecular genetics, meningiomas occur with greater frequency in genetic conditions such as neurofibromatosis Type 2 (NF2)[105,106] and multiple endocrine neoplasia Type 1 (MEN1).[4] Nearly all NF2-associated meningiomas, and many sporadic meningiomas, have mutations of the NF2 gene.[118] Nevertheless, phenotypic NF2 accounts for only a small minority (approximately 1%) of meningiomas. MEN1 has also been reported to carry an increased risk for meningioma, although with less likelihood of aberration at the NF2 gene locus.[4] How-

ABBREVIATIONS CGE = cobalt gray equivalent; EBRT = external beam radiation therapy; EORTC = European Organisation for Research and Treatment of Cancer; GTR = gross-total resection; MEN1 = multiple endocrine neoplasia Type 1; NF2 = neurofibromatosis Type 2; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology; RTOG = Radiation Therapy Oncology Group; SRS = stereotactic radiosurgery; STR = subtotal resection.

SUBMITTED August 1, 2013. **ACCEPTED** July 9, 2014.

INCLUDE WHEN CITING Published online October 24, 2014; DOI: 10.3171/2014.7.JNS131644.

DISCLOSURE Dr. Rogers is principle investigator for a meningioma clinical trial (no. RTOG-0539) and received a research grant from the National Cancer Institute in support of the trial. Dr. Raizer has served as a consultant to Roche, EMD Serano, Stemline, and Novartis; has received clinical or research support for this study from Novartis and Roche; and has served on the speakers bureau for Genentech.

ever, there is no clear documentation that NF2- or MEN1-associated meningiomas behave more aggressively than their sporadic counterparts.

Incidental, asymptomatic, radiologically presumed meningiomas appear to behave less aggressively[12,139] and may be managed with observation, during which treatment may be withheld until symptoms develop, sustained growth occurs, or concerns of encroachment on sensitive structures arise.[91] The focus of this paper is on larger, symptomatic meningiomas that undergo surgery or other definitive management options stratified by tumor grade, and not a detailed review of incidental, untreated meningiomas. Indeed, the grade of an incidental, observed meningioma is unknown, and its natural history may differ considerably from the larger, symptomatic tumors selected for definitive treatment. Studies have been undertaken to define the natural history of incidental meningiomas, and these results have been described in other papers.[12,43,88,89,98,139] Further systematic investigations are warranted to delineate which patients are best served by observation, how such observation should be tailored, which subgroups are at higher risk for tumor growth or symptom development, and whether long-term patient outcomes differ between surveillance and early definitive treatment.

Many questions remain regarding the selection and timing of treatment, especially in cases of recurrent meningioma or newly diagnosed high-grade meningioma (WHO Grade II [atypical] or Grade III [malignant] meningioma). For patients undergoing definitive therapy, complete resection has been the standard for meningioma, but there is a significant subset of patients who are not successfully managed by surgery alone, or in whom a complete resection is not possible due to the relationship of the tumor to eloquent anatomy. The potential for recurrence, whether following subtotal resection (STR) or gross-total resection (GTR), is well recognized in the literature.[18,84,115,130,132,142] Limitations associated with an initial treatment strategy of resection alone are even more apparent for patients with recurrent or high-grade meningioma.[2,75] The current WHO criteria[107] have improved the prediction of risk of tumor recurrence, but there remains significant uncertainty. Moreover, the relevance of the original (pre-MRI) Simpson classification based on the extent of resection has been questioned in the MRI era.[18,97,138,140] In particular, the surgeon's observations at the time of surgery are critical for defining the difference, for example, between a Simpson Grade 1 and Grade 2 excision. Consequently, there needs to be updated agreement regarding how to report the extent of meningioma resection.

Another commonly used treatment for meningioma is radiation therapy, including single-session stereotactic radiosurgery (SRS), hypofractionated stereotactic radiation therapy, and conventionally fractionated external beam radiation therapy (EBRT). A growing number of series have evaluated the use of SRS or EBRT as an adjuvant to surgery after STR for treatment of recurrent low-grade or high-grade meningioma, or as an alternative to surgery. When radiation therapy is used as an alternative to surgery, however, there is no tissue available for grading, or ability to assign a proliferative index or otherwise assess prognosis by histopathological or molecular measures. These studies, which we recognize are largely retrospective or single arm in design, as will be reviewed in this paper, have suggested improved tumor control compared with surgery alone or with observation. At present the most appropriate patients, tumor target volumes, radiation doses, and fractionation schemes are still undefined by prospective trials.

At 5 years, WHO Grade II and III meningiomas carry a 5- to 10-fold greater risk of progression than their initially diagnosed WHO Grade I counterparts.[104] These tumors can readily become refractory to treatment and entail considerably higher rates of cause-specific mortality. WHO Grade III (anaplastic) meningiomas have short recurrence-free intervals and high mortality rates. Pharmacological approaches, whether adjuvant or primary, are desirable, but have met with limited results. Consequently, considerable opportunity exists for the development of systemic or targeted agents for the treatment of high-grade meningiomas.

As a prelude to discussing outcomes of meningioma by WHO grade, it is important to note that the currently used grading criteria were developed and amended over the course of the last 2 decades. In 1993, the WHO attempted to codify and standardize meningioma grading; previously, many differing grading systems were in use.[36,41,80,104] The 1993 standards were an important advance, but were subject to considerable subjectivity. The 2000 and 2007 WHO iterations are less vague and more reliably applicable, but much of the pertinent literature is based on prior grading schemes. This renders comparisons among many publications difficult and tenuous.

It is also important to recognize that the reported incidence of all grades of meningiomas has varied substantially over time and by the method of meningioma identification, from 1 to 8.4 per 100,000 people.[76] Considering both microscopically confirmed and presumed tumors, a recent analysis reported an incidence of 3 to 3.5 per 100,000.[47] Adjusting for increases in population in the US, approximately 150,000 persons are currently diagnosed with meningioma.[15,21] Outcomes may vary according to histological and molecular genetic findings, tumor size and location, presenting clinical characteristics, and even the method of identification.

Recognition of the limitations of existing methods to evaluate outcomes of neurooncology patients led to the initiation of an international effort to develop consensus response and outcome evaluation criteria, particularly in the setting of prospective clinical research. This Response Assessment in Neuro-Oncology (RANO) working group consists of a multidisciplinary group of experienced clinical researchers, including neurooncologists, neurosurgeons, radiation oncologists, neuroradiologists, neuropsychologists, and experts in quality of life measures. Open meetings of RANO have included representatives from government, funding and regulatory bodies, and members of the drug and device industry. Recommendations made by the RANO working group are based on expert consensus opinion rather than Level 1 or Level 2 evidence. The primary purpose of this expert opinion process is to recommend a common set of definitions to

be used in the conduct of clinical research in neurooncology, in this case meningiomas. Previous reviews conducted by the RANO working group have focused on high- and low-grade gliomas, brain metastases, clinical trial design, and surgical applications of novel outcome measures.[66,67,117,147,148,151,153]

Appreciating these important qualifications, this overview examines published treatment outcomes, underscores deficiencies in our meningioma-related knowledge base, provides a foundation for response assessment (for which a future RANO publication is in progress), and suggests opportunities for future research. This paper focuses on surgery and radiation therapy; a companion article will appraise developments and opportunities with systemic therapies.

Methods

A PubMed literature search encompassing the years 2000 through 2013 for all English-language publications reporting clinical outcomes for patients with surgically or radiotherapeutically treated meningiomas was undertaken. Terms employed in the search were meningioma in multiple combinations that included surgery, radiation therapy, radiosurgery, survival, disease-free survival, progression-free survival, local control, tumor or WHO grade, pathology, atypical, anaplastic, malignant, and derivatives or synonyms of these terms. Bibliographies from the publications identified within PubMed were reviewed to identify further applicable articles. For outcome measures, surgery articles were included if the extent of resection and tumor grade were specified. Radiation therapy publications were included if radiation dose and technical details were described; radiosurgery publications were subject to these same constraints.

Reports were tabulated by year, number of patients, treatment technique, tumor location, mean or median follow-up, histological grade, and outcome measures. For patients receiving surgery, the extent of resection was collected, and for patients receiving radiation therapy or radiosurgery, dose and target volume definitions (when available) were recorded. Applicable outcome measures were recorded, along with their respective time points. The most consistently reported measure was progression-free survival (PFS) at 5 years, and when possible this was used as a unifying end point.

Results

WHO Grade I (Benign) Meningioma

Meningiomas have long been recognized as the most common nonglial intracranial tumors.[11] Recent data reveal that they are, in fact, the most frequently reported primary intracranial neoplasms,[15] accounting for 33.8% of all such tumors.[10] The majority of meningiomas are benign. With more uniform adoption of the current WHO 2007 standards, approximately 65% to 80% are Grade I (Fig. 1).[104,155]

Surgery

Since the publication of the seminal work of Simpson, maximal resection has been the objective of surgical management for meningiomas. Simpson correlated the extent of resection of tumor, associated dural attachments, and any hyperostotic bone to local recurrence risk and defined 5 grades of resection, which were associated with distinct rates of recurrence. These so-called "Simpson Grades" and their respective recurrence rates are summarized in Table 1.[128] The completeness of surgical removal has consistently been identified as an important prognostic feature,[18,22,112,132] and the majority of centers continue to use Simpson's criteria.

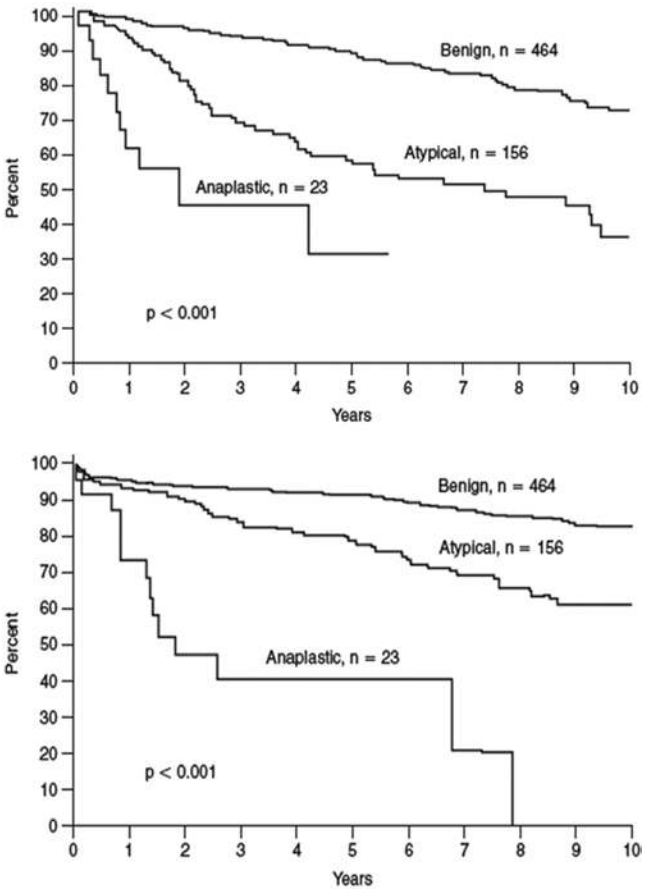

FIG. 1. Recurrence-free survival **(upper)** and overall survival **(lower)** for 643 patients with meningioma stratified by WHO grade. Among the 643 patients studied, 464 (72.2%) had a Grade I meningioma, 156 (24.3%) a Grade II meningioma, and 23 (3.6%) a Grade III meningioma.[104] From: *Russell & Rubinstein's Pathology of Tumors of the Nervous System* (7th ed.). By R.E. McLendon, M.K. Rosenblum, and D.D. Bigner. Copyright (2006) by Hodder Arnold, reproduced by permission of Taylor & Francis Books UK.

Sughrue and colleagues challenged the applicability of the Simpson classification in the present era. In 373 patients with WHO Grade I meningioma followed for a median of 3.7 years, they found no significant differences in 5-year PFS following Simpson Grade 1–4 resections, with 5-year PFS results of 95%, 85%, 88%, and 81%, respectively (p value was nonsignificant).[138,140] Similar findings were reported previously by Condra et al.,[18] and more recently by Oya et al.[97] These studies, while identifying no difference in local control after Simpson Grade 1–3 resections, did reveal shorter PFS following Simpson

TABLE 1. Simpson grades of resection, as derived from a series of 265 patients[128]

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 (e.g., invaded or hyperostotic bone)	29
4	Partial resection of tumor	44
5	Simple decompression (biopsy)	—

Grade 4 surgery.[18,97] A large series of 391 patients with convexity meningiomas studied by Hasseleid et al., expressly to address modern challenges to the predictive value of the Simpson resection grading system, identified significant outcome differences between Simpson Grade 1, Grades 2+3, and Grades 4+5,[44] which served to support the continued applicability of Simpson's criteria.

Gross-total resection (Simpson Grades 1–3) remains the prevalent objective of surgery for meningioma and is achieved in approximately one-half to two-thirds of patients in surgical series inclusive of meningiomas located in a variety of intracranial sites[84,112] and in more than 95% of convexity meningiomas.[87] For benign meningioma, GTR is considered definitive therapy.[18,84,112,132] However, with extended follow-up, recurrences in this setting are not infrequent.[1,18,84,130,132,142] In 5 separate series, rates of local recurrence after GTR ranged from 7%–23% at 5 years, 20%–39% at 10 years, and 24%–60% at 15 years (Table 2). The higher rates documented in the most recent of these analyses likely reflect the current use of serial evaluation with modern neuroimaging such as MRI.[130]

Subtotal resection (Simpson Grades 4 and 5) carries substantially higher rates of progression in many studies, even in benign meningioma. As shown by the 7 studies summarized in Table 3, local progression rates following STR vary from 37% to 62% at 5 years, to 52% to 100% at 10 years, and 70% or greater at 15 years. Condra and colleagues also found that STR affected cause-specific survival. Their patients who underwent STR alone experienced a 15-year cause-specific survival rate of 51%, significantly inferior to 88% after GTR and 86% after STR in addition to radiation therapy ($p = 0.0003$).[18] In a recent evaluation of clinical and molecular prognostic features of meningioma, Jensen and Lee reported that STR was associated with both poorer PFS and overall survival.[54] In spite of these reports, observation remains commonplace following STR. A Mayo Clinic series detailed 581 patients, 116 (20%) of whom underwent STR; only 10 (9%) of these patients received adjuvant radiation therapy.[132]

Patients with WHO Grade I meningioma have lengthy survival expectations (Fig. 1), and thus long-term studies are required to fully understand the risks of progression and death. In studies that have included prolonged evaluation with MRI, higher than expected rates of local progression have been identified[130] (Table 3). Moreover, recurrent meningioma exhibits a several-fold increased risk of progression and a shorter interval to progression than newly diagnosed tumors.[18,83,84,142] Miralbell et al. reported an 8-year PFS rate of 11% in recurrent tumor with surgery alone, compared with a rate of 78% following a combination of surgery and adjuvant EBRT.[83] Taylor et al. found a 5-year PFS rate of 30% with surgery alone for recurrent meningioma, compared with 88% for surgery and EBRT; they also reported 5-year overall survival rates of 45% and 90%, respectively.[142] These data support the need for prospective clinical investigation of methods to prevent recurrence and provide impetus for research into clinical, imaging, histopathological, and molecular predictors of response to treatment and to tumor progression.

Radiation Therapy

Multiple retrospective studies have demonstrated that various forms of radiation therapy, including SRS and EBRT, can provide improved and durable local control in selected patients with meningioma. Radiation therapy has most commonly been used as an adjunct to surgery following STR, as treatment for recurrence, or for tumors of high-grade histology. Additionally, as shown in Tables 4 and 5, many studies document excellent local control with SRS or EBRT as a primary modality. In these stud-

TABLE 2. Five single-institution series with prolonged follow-up, documenting rates of recurrence following GTR alone of benign meningiomas

Authors & Year	Institution	No. of Patients	Local Recurrence Rate (%)		
			5-Yr	10-Yr	15-Yr
Mirimanoff et al., 1985	MGH	145	7	20	32
Taylor et al., 1988	University of Florida	90	13*	25*	33*
Condra et al., 1997	University of Florida	175	7	20	24
Stafford et al., 1998	Mayo Clinic	465	12	25	—
Soyuer et al., 2004	MD Anderson	48	23	39	60*
Total		923	7–23	20–39	24–60

MGH = Massachusetts General Hospital.

* Data extracted from graph.

TABLE 3. Seven single-institution series with prolonged follow-up, assessing rates of recurrence following STR alone of benign meningiomas

Authors & Year	Institution	No. of Patients	Local Progression Rate (%)		
			5-Yr	10-Yr	15-Yr
Wara et al., 1975	UCSF	58	47	62	—
Barbaro et al., 1987	UCSF	30	40*	100*	—
Mirimanoff et al., 1985	MGH	80	37	55	91
Condra et al., 1997	University of Florida	55	47	60	70
Miralbell et al., 1992	MGH	79	40	52†	—
Stafford et al., 1998	Mayo Clinic	116	39	61	—
Soyuer et al., 2004	MD Anderson	32	62	82*	87*
Total		450	37–62	52–100	70–91

UCSF = University of California, San Francisco.
* Data extracted from graph.
† 8-year progression.

ies, radiation therapy was used predominantly for tumors in locations that are difficult to surgically access, such as the optic nerve sheath or cavernous sinus, and for patients regarded as inoperable for medical reasons or for those who chose primary radiation therapy over surgery.[31,63,64,68,73,77,101,113,123] These studies show that radiation therapy achieved long-term local control in 68% to 100% of WHO Grade I or presumed Grade I meningiomas at 5 to 10 years, including patients treated postoperatively, primarily, or following recurrence. Results varied somewhat by treatment era, tumor size and location, and clinical setting.

Stereotactic Radiosurgery

Stereotactic radiosurgery was developed more recently than fractionated EBRT, and over the past 2 to 3 decades has been used with increasing frequency. Stereotactic radiosurgery has been used after STR or for recurrence,[58,62,133] and as a definitive primary treatment.[31,113–115] Table 4 includes 35 studies of SRS and demonstrates that local control was achieved in the majority of patients at 5 to 10 years.

Stereotactic radiosurgery is considered most effective for patients with small meningiomas, typically those that are less than 3 cm in diameter or 10 cm^3 in volume, those with distinct margins, and those at sufficient distance from functionally important brain, nerves, and other critical structures to permit safe delivery of an adequate target dose. For WHO Grade I meningioma, excellent local control has consistently been achieved with 12 to 16 Gy (Table 4). Ganz and colleagues noted that a minimum peripheral tumor dose of 10 Gy or less was associated with higher failure risk, compared with a dose of at least 12 Gy.[32] Stafford et al. reported no reduction in local control at 5 years with tumor margin doses of less than 16 Gy as compared with doses greater than or equal to 16 Gy.[133] Similarly, Kondziolka et al. reported no improvement with marginal doses greater than 15 Gy versus less than 15 Gy.[60]

With respect to tumor size, DiBiase and colleagues reported a 91.9% 5-year disease-free survival for patients with meningiomas less than 10 cm^3 (equivalent diameter 2.7 cm), as opposed to 68% for larger tumors.[24] Kondziolka et al. reported excellent outcomes with SRS for meningiomas up to a diameter of 3.0 cm or a volume of 7.5 cm^3.[60] Likewise, other authors have found excellent local control and fewer radiation-related complications with smaller meningiomas, with complications in 4.8% of patients with tumors in the smallest quartile (< 3.2 cm^3) but in 22.6% in the largest quartile (> 9.6 cm^3).[113,114]

Pollock et al. reported on 188 patients with benign or presumed benign meningiomas treated using either surgery or SRS alone. With a median follow-up of 64 months, 7-year PFS with SRS and Simpson Grade 1 surgery were equivalent (95% and 96%, respectively). However, SRS resulted in superior tumor control when compared with less extensive surgery. The authors concluded that SRS should be a primary option when Simpson Grade 1 resection is unlikely.[115] In an updated analysis of primary SRS, Pollock and colleagues found 10-year local control was 99.4%, using a mean tumor margin dose of 15.8 Gy. No patient developed marginal recurrence. These results suggest that Grade I meningioma can often be accurately defined and well controlled with SRS as primary therapy. However, emphasizing the requirement for prolonged evaluation, 2 patients developed local progression more than 12 years after SRS.[113,114]

SRS for meningioma has traditionally involved a single session, but reports of multisession SRS are emerging.[17,33,69,73,86,144] These studies appear to demonstrate comparable local control to single-fraction treatment, with perhaps fewer side effects and a lower incidence of symptomatic edema, particularly for nonbasal/parasagittal or large meningiomas. In 1 of these reports, Unger et al. reported on 173 patients and found that symptomatic edema was significantly less common following multifraction SRS (typically 25 Gy in 5 fractions) than single-session SRS (median 15 Gy); the respective 2-year actuarial risks were 3.2% and 12.5%. Single-session SRS and tumor volume greater than 4.9 cm^3 were significant predictors of symptomatic edema.[144]

Girvigian et al. published a study involving 30 patients with convexity or parasagittal meningiomas, 14 treated with single-fraction and 16 with multifraction SRS. Multifraction treatment was typically 25 Gy in 5 fractions, and

TABLE 4. Thirty-five studies of SRS, largely for WHO Grade I or presumed Grade I meningiomas

Authors & Year	No. of Patients	Technique	Location	Mean FU (mos)	Mean/Median Dose (Gy)	5-Yr/10-Yr PFS (%)	Clinical Improvement (%)	Tumor Regression (%)	Complications (%)	Mean/Median Tumor Vol (cm^3)
Roche et al., 2000	80	GKRS	Cavernous sinus	30.5	14	92.8/—	27	31	4	5.8
Shin et al., 2001	40	GKRS	Cavernous sinus	42	18	91.3/91.3	—	37.5	2.5	4.3
Stafford et al., 2001	190	GKRS	All	47	16	93/—	8	56	13	8.2
Eustacchio et al., 2002	121	GKRS	Skull base	72	13	99/—	44.6	60	5	6.8
Lee et al., 2002	159	GKRS	Cavernous sinus	35	13	93/93	29	34	5	6.5
Nicolato et al., 2002	111	GKRS	Cavernous sinus	48.2	14.8	96/—	66	61	4.5	8.1
Spiegelmann et al., 2002	42	LINAC	Cavernous sinus	36	14	97.5/—	22	60	16.7	8.2
Flickinger et al., 2003	219	GKRS	All	29	14	93.2/—	—	—	8.8	5
Iwai et al., 2003	42	GKRS	Cavernous sinus	49	11	92/—	29	59.5	4.7	12.4
Pollock et al., 2003	62	GKRS	All	64	17.7	95/—	13	—	10	7.4
Roche et al., 2003	32	GKRS	Petroclival	56	13	100/—	58	12.5	9.3	—
Chuang et al., 2004	43	LINAC	Skull base	74.5	17	89.7/—	16	37	11	4.5
DiBiase et al., 2004	137	GKRS	All	54	14	86.2/—	—	28	8.3	4.5
Kreil et al., 2005	200	GKRS	Skull base	94	12	98.5/97	41.5	56.5	2.5	6.5
Pollock et al., 2005	49	GKRS	Cavernous sinus	58	15.9	100/—	26	59	14	10.2
Zachenhofer et al., 2006	33	GKRS	Skull base	103	17	94/—	44	36	12	—
Davidson et al., 2007	36	GKRS	Skull base	81	16	100/94.7	44	14	2.8	4.1
Hasegawa et al., 2007	115	GKRS	Cavernous sinus	62	13	94/92	46	—	12	13.8
Kollová et al., 2007	331	GKRS	All	68	12.5	98/—	62	70	10	6.3
Han et al., 2008	63	GKRS	Skull base	77	12.7	90.2/—	45	44	17	6.3
Iwai et al., 2008	125	GKRS	Skull base	86	12	93/83	13	46	7.2	8.1
Kondziolka et al., 2008	972	GKRS	All	48	14	97/87	11	42	8	7.4
Kondziolka et al., 2009	125	GKRS	Convexity	31	14	86/—	—	26	9.6	7.6
Bledsoe et al., 2010	116	GKRS	All	70	15.1	99/92	—	—	23	17.5
Flannery et al., 2010	168	GKRS	Petroclival	72	13	95/—	26	49	14	7.7
Korah et al., 2010	41	LINAC	All	60	14	94/94	—	—	2.4	4.5
Skeie et al., 2010	100	GKRS	Cavernous sinus	82	12.4	94/91.6	21	22	6	7.4
Zada et al., 2010	116	GKRS	All	75	16	99/84	—	26	8	3.4
Williams et al., 2011	138	GKRS	Parasellar	84	13.7	95.4/69	—	78	10	7.5
Hayashi et al., 2011	66	GKRS	Skull base	46	12	99/—	—	82	1	6.6
dos Santos et al., 2011	88	LINAC	Cavernous sinus	87	14	92.5/82.5	51.1	73.8	19.3	—
Santacroce et al., 2012	4565	GKRS	All	63	14	95.2/88.6	53.5	58	6.6	4.8
Unger et al., 2012	173	LINAC	All	21	15*	89.3/—	—	—	8.5†	4.7
Pollock et al., 2012	251	GKRS	All	62.9	15.8	99.4/99.4	—	72.1	11.5	7.7
Starke et al., 2012	255	GKRS	Skull base	78	14	96/79	—	49	5.1	5.0

FU = follow-up; GKRS = Gamma Knife radiosurgery; LINAC = linear accelerator.

* Fifteen Gy was the median dose with single-fraction radiosurgery; with multifraction radiosurgery, it was 25 Gy in 5 fractions.

† Symptomatic edema risk for all patients combined (12.5% with single fraction and 3.6% with multifraction radiosurgery).

TABLE 5. Thirty-five studies of fractionated EBRT for patients with largely WHO Grade I or presumed Grade I meningiomas

Authors & Year	No. of Patients	Technique	PFS (%)				Clinical Improvement (%)	Tumor Shrinkage (%)	Late Toxicity (%)	Time Point (yrs)
			GTR	STR	STR+RT	RT Alone				
Adegbite et al., 1983	114	EBRT	74	34	82					10
Mirimanoff et al., 1985	225	EBRT	80	45						10
Barbaro et al., 1987	135	EBRT	96	40	68				0	Crude
Taylor et al., 1988	132	EBRT	77	18	82					10
Glaholm et al., 1990	117	EBRT	96	43	77	46	38			10
Miralbell et al., 1992	115	EBRT		48	88				16	8
Mahmood et al., 1994	254	EBRT	98	62						5
Goldsmith et al., 1994	117	EBRT			77 98*				3.6	10
Peele et al., 1996	86	EBRT		52	100				5	Crude
Condra et al., 1997	246	EBRT	80	40	87				24	10
Stafford et al., 1998	581	EBRT	75	39						10
Nutting et al., 1999	82	EBRT			83				14	10
Vendrely et al., 1999	156	EBRT			79		59	29	8	
Pourel et al., 2001	26	EBRT			76				2.2	8
Dufour et al., 2001	31	EBRT			93		71	29	3.2	10
Jalali et al., 2002	41	FSRT			100		26.8	22	12.1	3
Uy et al., 2002	40	IMRT			93			23	5	5
Pirzkall et al., 2003	20	IMRT			100		60	25	0	3
Soyuer et al., 2004	92	EBRT	77	38	91				2.5	10
Selch et al., 2004	45	FSRT			97		20	18	0	3
Milker-Zabel et al., 2005	317	IMRT			89		42.9	23	0	10
Henzel et al., 2006	224	FSRT			97		43.4	46	0	3
Milker-Zabel et al., 2007	94	IMRT			94		39.8	20	4	4.4
Hamm et al., 2008	183	FSRT				93		23.2	2.7	3
Litré et al., 2009	100	FSRT			94	94	50–81	9	0	5
Korah et al., 2010	41	FSRT				94			3	5
Metellus et al., 2010	53	FSRT			94	94	58.5	30	1.9	10
Bria et al., 2011	60	FSRT				95	60			1
Minniti et al., 2011	52	FSRT				96 93	20	23	5.5	3 5
Mahadevan et al., 2011	16	FSRT				100		19	4	2
Morimoto et al., 2011	31	FSRT				87		1		5
Onodera et al., 2011	27	FSRT				96.2				5.3
Ohba et al., 2011	281	FSRT/SRS	88.3	63.7	92.3					5
Tanzler et al., 2011	146	EBRT/FSRT/SRS			96 93	99 99			6.8	5 10
Paulsen et al., 2012	109	FSRT				98	21	5		5

FSRT = fractionated stereotactic radiation therapy; IMRT = intensity-modulated radiation therapy; RT = radiation therapy.
* Ten-year PFS rate of 98% with treatment after 1980 when CT and MRI began to be used for treatment planning, versus 77% before 1980.

was used for larger tumors. Symptomatic edema occurred in 43% following single-fraction SRS, as opposed to 6.3% (1 patient) after multifraction SRS, and this patient had pretreatment edema. Single doses of more than 14 Gy and larger tumor volume were predictors of edema.[33]

Columbo et al. reported on 49 patients who received single-fraction SRS (11–13 Gy) and 150 patients with tumors close to critical structures and/or greater than 8 cm^3 in volume who were treated with multifraction SRS (14–25 Gy in 2–5 fractions). For the entire cohort, 5-year PFS was 93%. Columbo et al. observed very few treatment-related complications, even in patients with large tumors, and maintained that with the use of multifraction SRS they were able to treat 63 patients who could not have been treated by single-fraction techniques.[17]

Fractionated EBRT

Historically, meningiomas have been considered resistant to irradiation, probably due to infrequent documentation of tumor regression following the use of EBRT. EBRT

was also believed to produce considerable side effects, to potentiate malignant degeneration, and indeed to cause meningiomas.[58,84,121,137] These concerns likely remain an issue today, and as a consequence many patients with inoperable or subtotally resected meningioma are managed by observation.[3,132] A recent publication by Sughrue et al. reported the outcomes of 373 patients with newly diagnosed WHO Grade I meningiomas, the preponderance located at the skull base, treated using surgery alone. Simpson resection grades were Grade 1 in 88 patients (23.6%), Grade 2 in 114 (30.6%), Grade 3 in 57 (15.3%), and Grade 4 in 114 (30.6%),[138,140] indicating that many patients with a subtotally resected meningioma continue to be managed without adjuvant therapy.

Regarding the risk of radiation-associated tumor dedifferentiation (i.e., transformation to a higher tumor grade), reliable estimates are difficult to ascertain. Dedifferentiation has not been definitively linked to radiation therapy. Furthermore, advancing tumor grade is the natural history of a subgroup of recurrent or progressive meningioma.[52,93] To establish radiation-induced malignant transformation, detailed histology prior to irradiation would be indispensable. Moreover, radiation is often used only after imaging-confirmed regrowth, without additional histological analysis. Thus, whether dedifferentiation results from irradiation or as a result of natural cellular evolution cannot be readily determined.[93] This raises the question of whether some advanced imaging surrogate of histology could be developed and used to help guide therapy and predict outcomes.

The risk of developing a meningioma after cranial irradiation has been reviewed by Strojan et al., who reported an actuarial risk of 0.53% at 5 years and 8.18% at 25 years.[137] This risk appears to be considerably smaller with modern, highly conformal therapy. Minniti et al. reported on 426 patients with pituitary adenoma treated using surgery and small-field EBRT and followed for 5749 person-years. The risk of a second brain tumor at 20 years was 2.4%. Of the 11 second tumors, 5 were meningiomas.[82] With even smaller field treatment using SRS, and with more than 9000 patients, Niranjan and colleagues estimated a second tumor risk of less than 1 per 1000.[93] This risk is smaller than that reported for the published series using larger field nonconformal EBRT, but with modern, highly conformal approaches to fractionated EBRT, improved outcomes relative to older series may be expected.

Outcomes data from 35 studies of EBRT for meningioma are described in Table 5. These studies, while retrospective in nature, provide evidence that EBRT can improve PFS when used as an adjunct to STR, as salvage treatment of meningioma at recurrence, or as primary therapy. Excellent long-term outcomes from primary EBRT are reported for optic nerve sheath meningiomas. For these tumors, surgery carries a high risk of visual complications and a high rate of local recurrence, whereas EBRT alone results in more favorable outcomes than observation, surgery, or surgery in addition to EBRT.[90,101,143] Moreover, patients with optic nerve sheath meningiomas commonly experience improved visual acuity following use of EBRT.[90,101,143,146]

Primary EBRT for intracranial meningiomas not involving the optic nerve sheath has also resulted in excellent local control, clinical improvement, and low rates of toxicity (Table 5). Tanzler et al. studied 88 patients treated with definitive EBRT (mean total dose 52.7Gy). The majority of patients were diagnosed on the basis of imaging findings alone. Median follow-up for living patients was 8 years, and 10-year local control was 99%.[141]

Technical improvements in the delivery of EBRT have favorably affected the outcome and side effects of this treatment modality. Treatment is now delivered with more precision and conformality, and improvements in local control have been documented. Goldsmith et al. and Milosevic et al. each substantiated improvements in local control with modern imaging.[35,36,80] Goldsmith found that, with immobilization techniques and with CT- or MRI-based planning, 10-year PFS improved from 77% to 98% ($p = 0.002$).[35,36]

Recommended EBRT doses for benign meningiomas are generally 50–55 Gy with fraction sizes of 1.8–2.0 Gy,[18,35] but a dose-response relationship has not been unequivocally established. Goldsmith et al. reported that doses greater than 52 Gy resulted in improved 10-year local control, but this effect was not substantiated on multivariate analysis.[36] Winkler and colleagues found no clear dose-response from 36 to 79.5 Gy (1.5–2.0 Gy per day).[156] A common dosing schedule for WHO Grade I meningioma is 54 Gy in 27 to 30 fractions, although for meningioma of the optic nerve sheath or near the anterior visual pathway, lower total doses in the range of 50 Gy and even modestly lower doses per fraction have achieved good results.[90,126] Figure 2 displays preoperative and postoperative MR images and the dosimetry plan CT for EBRT on a patient with a subtotally resected WHO Grade I meningioma. The prescription dose was 5400 cGy in 30 fractions.

Radiation treatment-related edema has rarely been reported with EBRT. In 35 studies involving 4389 patients (Table 5), less than 0.5% of patients were reported to have developed treatment-related edema. It should be noted, however, that many studies did not specifically assess edema, and some patients with treatment-related edema, especially if asymptomatic, may have escaped detection. However, Selch and colleagues specifically examined the rate of treatment-related edema in 45 patients and found no cases of post-EBRT edema with a median follow-up of 3-years.[124] Tanzler et al. studied 146 patients treated with EBRT and 2 (1.4%) developed edema.[141] It appears that edema is a less likely consequence of EBRT than of single-fraction SRS. Delayed neurotoxicity is also an important consideration, but little is known with specific reference to patients with meningioma, so this represents an avenue for further research.

WHO Grade II (Atypical) Meningioma

Although for decades Grade II meningiomas were identified in only about 5% of cases, with the adoption of the 2000 and 2007 WHO criteria, they now constitute 20%–35% of newly diagnosed meningiomas.[15,102,104,155] Given this magnitude of change in their identification, investigation is needed to redefine the natural history expectations for these tumors and to better define the results of treatment. Furthermore, assessment is needed to determine how uniformly the new WHO diagnostic criteria are

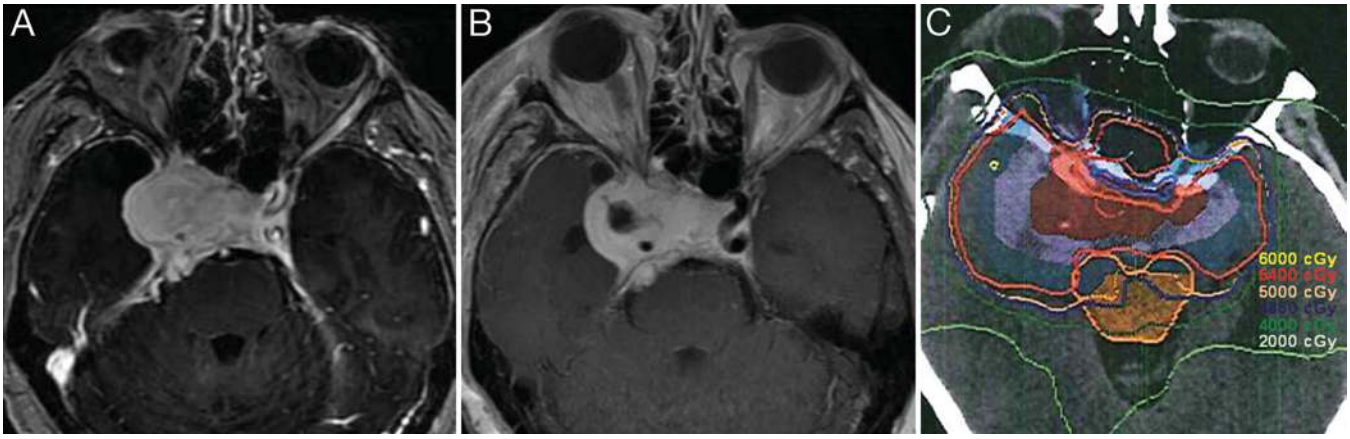

FIG. 2. Preoperative **(A)** and postoperative **(B)** axial MR images as well as the dosimetry plan CT scan **(C)** for EBRT in a patient with a subtotally resected WHO Grade I meningioma. The prescription dose was 5400 cGy in 30 fractions (180 cGy per fraction). Courtesy of Heyoung McBride, MD, and Terry Thomas, MS, Barrow Neurological Institute, Phoenix, Arizona. Figure is available in color online only.

being implemented, and to define the rates of interobserver and interinstitutional concordance in diagnosis. These investigations are crucial because, as shown in Fig. 1, atypical meningioma carries a 7- to 8-fold increased risk of recurrence at 5 years and an increased rate of mortality compared with WHO Grade I meningioma.[104]

Surgery

When evaluating the impact of treatment on atypical meningioma, it is critical to keep in mind that the literature consists of retrospective reports, and that most include patients diagnosed using pre-WHO pathological criteria, which underreported the incidence of atypical meningioma. Both the recently completed Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) prospective trials included central review of pathology, and analysis of their pathological material is eagerly awaited. There is general agreement, but not consensus, that STR alone is insufficient treatment for WHO Grade II meningioma. Surveys among neurosurgeons in Germany and the United Kingdom indicated that 26% and 41%, respectively, do not recommended adjuvant therapy after STR of an atypical meningioma.[74,127] Another single-institution series reported a 10-year local control rate of 17% following STR of atypical meningioma but could not document a significant benefit associated with the use of postoperative radiation therapy.[37] In general, neurosurgeons have used the strategy of serial re-resection to manage Grade II meningioma recurrence.

There is considerably less agreement regarding adjuvant treatment after GTR. In Germany, 84% (47 of 56) of centers recommended surgery alone for initially diagnosed, gross-totally resected WHO Grade II meningioma,[127] similar to centers in the United Kingdom, in which 80% made the same recommendation.[74] A number of other reports have suggested that GTR alone is sufficient for these patients.[37,70,72,99,102] Jääskeläinen reported a 38% 5-year local recurrence rate after GTR and did not find that adjuvant radiation therapy was of utility.[52] However, no randomized trials have been completed; many of the studies in the literature had small cohorts, used pre-WHO 2000 grading criteria, included patients with newly diagnosed and recurrent tumors, or used radiation therapy doses that were, as will be discussed subsequently, likely too low to be effective.

Employing WHO 2000/2007 criteria and higher EBRT doses, Aghi et al. analyzed 108 patients with atypical meningioma. Following Simpson Grade 1 surgery alone, the 5-year local recurrence rate was 50%.[2] A more recent report by Komotar et al. reviewed outcomes among 45 patients, each with a gross-totally resected atypical meningioma. Gross-total resection was defined as Simpson Grade 1 or 2, confirmed by postoperative MRI. Thirty-two (71%) of their 45 patients were treated initially with surgery alone and experienced a 5-year actuarial risk of recurrence of 55%.[59]

The clinical impact of tumor recurrence in patients with atypical meningioma appears to be more significant than in patients with WHO Grade I tumors. Mair et al. found that neither the extent of salvage resection nor the use of radiation therapy was predictive of outcome for patients with recurrent Grade II meningioma.[72] Aghi et al. reported a 10-year disease-specific survival rate of 69% after first recurrence.[2] With a median follow-up of 44.1 months, the study of Komotar and colleagues noted crude overall survival of 69.2% following first recurrence, very similar to the study of Aghi et al.,[2] and concluded that recurrences resulted in shortened overall survival, as well as additional treatment burden.[59]

Radiation Therapy

Various forms of radiation therapy have been used for Grade II meningioma following STR, including SRS[5,55,129,133] and EBRT.[2,8,16,18,49,80] Even following GTR, many have advocated radiation therapy for these patients,[2,18,41,48,49,100,156] but others recommend observation.[37,72,102] Irradiation is also commonly employed as a primary modality for some meningiomas, but as there was no pathological confirmation it is unclear how many were WHO Grade II tumors. The determination of grade requires tissue confirmation, and there are very limited data on primary radiation therapy after biopsy alone.

Achieving local control for patients with atypical meningiomas is an important end point with radiation therapy and appears to be paramount. As aforementioned, Aghi et al. reported a 69% 10-year disease-specific survival rate after first recurrence.[2] Skeie and colleagues found that 6 of 7 patients with recurrence died of disease at a mean of 25 months after regrowth.[129] Stafford et al. noted that patients with prior surgery or EBRT fared worse, and that patients with recurrent atypical tumors continued to exhibit worse cause-specific survival despite aggressive salvage therapy.[133]

Stereotactic Radiosurgery

Reports of SRS for Grade II meningiomas are, with near exclusivity, in the settings of STR or recurrence, mostly the latter. Table 6 summarizes 8 series involving SRS for atypical meningiomas. Reported local control at 2 years and beyond spans a wide range, from 0% up to 90%, with most in the 50% to 80% range. These studies suggest that dose, target volume, and treatment timing are key elements in improving outcomes. Kano et al. reported that 5-year PFS for lesions treated using less than 20 Gy was 29.4%, compared with 68% for those receiving 20 Gy ($p = 0.0139$).[55] However, Stafford et al. identified a 5-year local control rate of 68% using a moderately lower dose (median 16 Gy, range 12–36 Gy), and found no clear correlation between SRS dose and local control.[133]

Attia and colleagues, studying dose and conformality index (treatment volume ÷ tumor volume) in residual or recurrent Grade II tumors, shed further light on this issue. Their median dose was 14 Gy (range 12–18 Gy). Local recurrence, defined as within 2 cm of the original tumor margin, developed in 48% at 5 years, with a median time to recurrence of 25 months. When the conformality index was considered, margin dose was not predictive of local control.[5] The mean conformality index was 1.7 in the patients who experienced recurrence and 4.6 in those who did not ($p = 0.038$). This raises the possibility that higher doses in some studies[55] might, in part, be a proxy for a larger conformality index.

This finding is supported by other studies showing that atypical meningiomas may recur outside of the SRS target, yet inside the resection bed. Huffmann et al. treated 15 patients with a median dose of 16 Gy. At 18 to 36 months, 9 were progression free, for a crude local control rate of 60%. Six (40%) progressed, 1 (17%) in field, but all within the surgical approach or resection bed.[48] Choi et al. reviewed 25 patients with Grade II meningiomas, with a median marginal dose of 22 Gy (range 16–30 Gy) in 1–4 fractions (median 1). Recurrence was identified in 9 patients: 3 (33%) within the targeted region (local failure), 5 (56%) elsewhere in the resection bed (regional failure), and 1 (11%) locoregionally.[13] These findings suggest that, for atypical meningioma, a volume beyond the residual or recurrent enhancement is at risk, and that this includes the entire tumor and resection bed. Further patterns of failure analyses will help define the best approaches to target definition.

Timing of treatment may also influence outcome. Choi et al. showed improved local control with immediate postoperative SRS (within 6 months of surgery) as opposed to SRS at recurrence or progression.[13] Harris and colleagues, defining "late" as after radiographic progression and "early" as after craniotomy without imaging evidence of progression, found a median time to neurological progression of 15 months after "late" SRS, compared with 61 months with "early" treatment.[41]

Multisession SRS has also been used for Grade II meningioma, often for larger or critically located tumors, involving for instance the anterior optic apparatus, or the sagittal sinus where edema more likely occurs after single-fraction SRS.[17,33,144] Local control results have been essentially equivalent to single-fraction therapy,[17] possibly with a lower risk of side effects.[17,33,144] Vernimmen et al. reported on multifraction SRS using protons. With a mean follow-up of 40 months, 88% of the patients remained under radiological control. With the multifraction approach, these investigators were able to treat larger tumors, up to 63 cm^3.[150] Presently, multifraction SRS data specific to atypical meningioma is limited, and its role and proper dose-volume constraints remain important research questions.

Fractionated EBRT

Several investigators have reviewed EBRT for atypical meningioma. Some have recommended EBRT irrespective of resection extent,[18,49,156] but others have questioned its benefit. Goyal et al. reported local control of 87% at 5 and 10 years among 22 patients. EBRT was used in 8 patients, with a median dose of 54 Gy, but did not significantly affect outcome.[37] Hoffman and colleagues identified 10 patients with Grade II meningioma; the postoperative recurrence rate was 50%. They suggested a benefit to EBRT, especially when radical surgery could not be achieved, and recommended a higher total dose of 60 Gy.[47]

Aghi et al. published an analysis of 108 patients with atypical meningioma and Simpson Grade I resection. One hundred (93%) underwent surgery alone, and 8 (7%) underwent surgery as well as EBRT (mean 60.2 Gy). The target volume was described as 1 cm beyond the resection bed. Five-year recurrence after GTR alone was 45%, but 0% following surgery with EBRT. This difference did not reach statistical significance ($p = 0.1$), perhaps due to the relatively small number of events. These investigators assessed the clinical consequences of recurrence and found that all 30 patients with recurrence ultimately received either EBRT or SRS, and 73% underwent repeat surgery, with a mean number of craniotomies of 2.7. Only 1 meningioma had transformed to WHO Grade III, but at 7 years 33% of the patients had died as a result of recurrence.[2]

Similarly, Komotar et al. reported on 45 patients with atypical meningioma who received a Simpson Grade 1 or 2 resection. Thirty-two underwent GTR alone and 13 had GTR with EBRT (median 59.4 Gy), to a target described as the tumor cavity as well as a 0.5 to 1.0 cm margin. After surgery alone, 13 patients (41%) experienced recurrence at a median of 19 months. After GTR and EBRT, 1 patient (8%) experienced recurrence at 52.5 months. Following GTR alone versus GTR and EBRT, the respective 6-year actuarial recurrence risks were 65% versus 20% ($p = 0.085$).[59] Other recent analyses have supported EBRT in this setting. Park et al. reported 5-year PFS rates of 46.4%

TABLE 6. Eight studies of SRS for atypical meningioma

Authors & Year	No. of Patients	FU (mos)*	Dose (Gy)*	Local Control (%)	Time Frame	Comments†
Stafford et al., 2001	13	47	16	68	5-yr actuarial	Majority were recurrent before SRS; 5-yr local control for Grade I = 93%; 5-yr overall survival = 76% for Grade II vs 92% for Grade I, worse cause-specific survival for Grade II. Predictors: prior surgery or EBRT, larger tumor volume, location (non-basal)
Harris et al., 2003	18	46	14.9	83	5-yr actuarial	Mean of 2 resections prior to SRS; 5-yr overall survival = 59%; better w/ smaller tumor volume & early SRS; median neurological progression 15 mos early SRS vs 61 mos late SRS
Huffmann et al., 2005	15	35	16	60	Crude 18–36 mos	67% recurrent before SRS; 6 progressed after SRS, only 1 in field after 15 Gy, but all w/in the surgical bed; "Recurrence was essentially outside the SRS field"
Kano et al., 2007	12‡	43	18	48.3	2-yr actuarial	All recurrent before SRS; 5-yr PFS 29.4% <20 Gy vs 63.1% at 20 Gy; 19 lesions progressed, 13 in field, & 6 out of field. Predictors: Grade III (vs II), dose <20 Gy (vs 20 Gy)
Attia et al., 2009	24	26	14	76 52 58	1-yr actuarial 2-yr actuarial 5-yr actuarial	Tumor volume & dose not predictive of local control, but conformality index was predictive; mean conformality index = 1.7 if recurrent vs 4.6 if no recurrence§
Skeie et al., 2010	7	82	12.4	0	Mean 43 mos	100 cavernous sinus meningiomas, 7 Grade II; 5/7 progressed w/in 15 mos. Predictors: Grade II, tumor volume, dose, & suboptimal coverage
Choi et al., 2010	25	28	22¶	90** 90** 62**	1-yr 2-yr 3-yr	15 treated immediately after STR, 10 after progression; 9 failures (3 local, 6 regional). Predictors: no. of recurrences, delayed SRS, age ≥60 yrs
Hardesty et al., 2013	32	52	14	94†† 73†† 62††	1-yr 3-yr 8-yr	Not significantly different from GTR or STR alone; no recurrence in 10 patients w/ GTR & SRS

* Mean or median.
† Suboptimal coverage defined as < 88%.
‡ Ten of the 12 had atypical primaries, 2 were anaplastic.
§ Conformality index = treatment volume ÷ tumor volume.
¶ Median marginal dose 22 Gy in 1–4 fractions (median 1).
** Percentages refer to locoregional control (i.e., SRS target and resection bed).
†† Data derived from graph.

with GTR alone, 77.9% with GTR and EBRT, 0% with STR alone, and 55.6% for STR and EBRT. Progression-free survival was improved by EBRT, regardless of the extent of resection.[100]

Others have reached different conclusions. Mair et al. suggested that EBRT was not appropriate following GTR, and advised SRS rather than EBRT following STR.[72] In spite of this contention, their report did confirm that EBRT improved PFS. Comparing surgery to surgery with EBRT, 4-year PFS rates were 13% following surgery alone versus 72% with surgery and EBRT ($p = 0.043$). These results were not stratified by extent of resection, and Mair et al. used a relatively low mean EBRT dose of 51.8 Gy in 28 fractions.[72] Hardesty and colleagues reported improved outcomes with GTR but no significant improvement in recurrence rate with radiation therapy (either EBRT or SRS) following "aggressive microsurgical resection" of an atypical meningioma. Gross-total resection, defined as Simpson Grade 1 or 2, was achieved in 58% of patients. Appreciating the lack of statistical significance, it is notable that no patient in this study treated with a GTR and postoperative radiation therapy experienced recurrence, with actuarial data extending 7 to 9 years.[40] In this series, the number and length of follow-up of patients managed with GTR and radiation therapy was limited. Their median radiation therapy dose, 54 Gy with 1.8- to 2.0-Gy fractions, as discussed below, may be lower than optimal, but even with this dosing, there were no recurrences in patients treated with GTR and radiation therapy.

A Surveillance, Epidemiology, and End Results (SEER)-based analysis by Stessin et al. reviewed 657 patients treated for nonbenign meningioma from 1988 to 2007.[135] Two hundred forty four (37%) received adjuvant EBRT. After controlling for WHO grade (II vs III), tumor size, extent of resection, and date of diagnosis (i.e., considering the 2000 WHO reclassification), EBRT was not found to impart a survival or disease-specific survival benefit. Paradoxically, they found significantly lower survival for patients receiving adjuvant EBRT than for those receiving no radiation, possibly reflecting a treatment selection bias for patients with poor overall prognosis. Stessin et al. did not analyze local control, and did not factor in EBRT doses or target definition parameters;[135] this may be of critical importance because higher EBRT doses appear to improve outcome for Grade II meningioma.

Park et al. found an improved PFS using a mean dose of 61.2 Gy.[100] Aghi et al. observed no local recurrences with 59.4 to 61.2 Gy,[2] and Komotar et al. had numerically better outcomes with a median EBRT dose of 59.4 Gy. The RTOG trial (no. 0539), which recently completed accrual, used 54 Gy in 30 fractions for newly diagnosed atypical meningioma following GTR, and 60 Gy in 30 fractions following STR or for recurrent Grade II tumors of any resection extent. The completed EORTC trial (no. 22042-26042) employed 60 Gy following a GTR and added a 10-Gy boost after STR. These trials will ultimately provide important guidance regarding dose escalation for atypical meningioma.

Studies of proton radiotherapy further illuminate questions of dose. Hug et al. published results of 15 patients with atypical meningioma. Approximately half of all patients received EBRT with photons and half combined photons and protons, with total doses from 40 to 72 cobalt gray equivalents (CGEs). Local control was significantly improved with doses greater than 60 CGE, with a 5-year local control rate of 90% with greater than 60 CGE, and 0% with less than 60 CGE. These authors noted improved results with combined photon and proton therapy, but this was not an independent factor, rather a reflection of higher doses with the use of protons.[49] Boskos et al. published outcomes on 24 patients with high-grade meningiomas, typically treated following STR. Nineteen meningiomas (79%) were WHO Grade II. Cause-specific survival at 5 years was 80% with greater than 60 Gy compared with 24% with less than 60 Gy ($p = 0.01$). There was a trend toward further improvement with doses greater than 65 Gy ($p = 0.06$).[8]

Optimal dosing regimens, and choices among varying radiation modalities, are important matters for further study. Dose escalation may have a role in treating high-grade meningioma, but caution with dose escalation is warranted. Using accelerated hyperfractionated EBRT with or without an SRS boost, Katz et al. found a high rate of complications with no improvement in tumor control.[56] Future research on radiation therapy dosing and other critical issues will be strengthened by uniform adoption of WHO grading standards and by studies that stratify patients into de novo and recurrent categories.

WHO Grade III (Anaplastic/Malignant) Meningioma

Less than 3% of newly diagnosed meningiomas are WHO Grade III (also termed anaplastic or malignant). Consequently, there are only about 300 newly diagnosed anaplastic meningiomas per year in the US.[47] With such rarity, firm conclusions regarding optimal treatment are problematic.

These are aggressive tumors with considerably poorer local control and overall survival than lower grade meningiomas. In studies used to determine WHO grading, median overall survival in patients with these tumors has been less than 2 to 3 years (Fig. 1).[108,109] There is little discrepancy in recommendations for aggressive treatment, which typically includes surgery and radiation therapy, but regarding the required extent of surgery, the preferred type of radiation therapy, and its dosing and target volume constraints, treatment remains controversial. Even with aggressive management, local control remains difficult to attain, and metastasis, although uncommon, can occur. Improved treatment paradigms are needed.

Surgery

In most cases of aggressive meningioma, surgery serves as the first-line therapy and helps establish a diagnosis. As is the case with lower grade meningiomas, recurrence corresponds to the extent of tumor removal.[27,37,99,108] However, the success of surgery alone has not been satisfactory. Jääskeläinen et al. reported a 5-year recurrence rate of 78% following GTR for patients with anaplastic meningioma, less than half of whom received any adjuvant therapy.[52] Among patients with malignant histology treated with surgery alone, Dziuk et al. encountered a 5-year PFS of 28% after GTR, and 0% after STR.[27] Most investigators now recommend adjuvant therapy.[28,113,138]

When a clear plane between the tumor and surrounding normal structures can be identified, GTR remains the goal of surgery for anaplastic meningioma.[140] Sughrue et al. recently analyzed resection extent for patients with WHO Grade III meningioma. All patients were also referred for postoperative EBRT. They found that heroic surgical efforts did not improve survival, and even compromised neurological outcome. Specifically, they found improved overall survival with near-total resection as opposed to GTR; near-total resection implied greater than 90% tumor removal.[140]

Surgery appears to be beneficial at recurrence as well. Correcting for other prognostic factors, Sughrue et al. found a survival benefit from repeat operation, with median survivals of 53 months with salvage surgery versus 25 months without ($p = 0.02$). All patients received EBRT, and some also received radiosurgery or brachytherapy. As with their patients in the de novo setting, near-total resection resulted in superior median survival compared with GTR (77 vs 42 months, respectively; $p = 0.005$).[140] In contrast, other investigators have found that the mode of salvage therapy for patients with WHO Grade III meningiomas did not significantly affect time to subsequent progression.[122]

Radiation Therapy

There are no randomized trials to document the efficacy of multimodality therapy for patients with malignant meningioma, but retrospective studies, using varying definitions of anaplasia, have reported measurable benefits.[18,27,80,122,130] As documented in Table 7, both EBRT and SRS have been used. Outcomes vary, perhaps in part by treatment technique, but also in relation to the extent of surgery, the histological grading standards employed, the extent and type of follow-up, and the timing of radiation treatment.

Stereotactic Radiosurgery

Some authors have argued that SRS is not indicated for malignant meningioma,[85] but several studies have reported outcomes with SRS (Table 7). Kondziolka et al. treated 29 WHO Grade III patients with postoperative SRS, using a mean margin dose of 14 Gy, and found PFS rates of 17% at 15 months and 9% (extrapolated from graph) at 5 years.[62] In a separate publication of convexity meningioma, the same group treated 5 WHO Grade III patients. With follow-up extending to 47 months, none maintained local control, and 4 of 6 died of tumor progression.[61]

El-Khatib et al. reported 7 patients with WHO Grade III meningioma, using a 14 Gy margin dose.[28] They found considerably higher rates of PFS, 57% at 3 years and 43% at 10 years. This study used similar tumor margin doses to Kondziolka et al. The mean target volumes were modestly smaller in the El-Khatib et al. study (4.8 vs 7.4 cm^3). Both studies included newly diagnosed and recurrent tumors. The Kondziolka study graded tumors based upon "previous histopathology" (often diagnosed before the advent of the WHO criteria), whereas El-Khatib et al. used the WHO 2007 criteria. These differences in diagnostic criteria may play a role in accounting for the differences in results.

Pollock and colleagues recently published their experience with 50 WHO Grade II or III patients, treated in both the de novo and salvage settings. Thirteen patients had anaplastic meningioma. Their median treatment volume was larger at 14.6 cm^3, and the median dose was modestly higher at 15 Gy. Disease-specific survival rates at 1 and 5 years for the WHO Grade III patients were 69% and 27%, respectively. These investigators did not specify PFS for malignant meningioma alone, but for their entire group of 50 high-grade tumors, PFS at 1 year was 76%, and at 5 years was 40%. For patients who had failed prior EBRT, PFS was lower, i.e., 19% at 3 years.[114]

Fractionated EBRT

The early experiences of Milosevic et al.[80] and Dziuk et al.[27] provide evidence of benefit from surgery followed by EBRT, and indeed for the use of EBRT initially rather than at progression, now accepted as a standard approach for anaplastic meningiomas. Milosevic et al. found that patients who received < 50 Gy experienced inferior cause-specific survival, as did those treated before 1975 (i.e., before CT-based planning).[80] Dziuk et al. found that EBRT improved 5-year PFS from 50% to 80% compared with surgery alone. When EBRT was added following initial resection, 5-year PFS significantly improved from 15% to 80%. They recommended a total EBRT dose of 6000 cGy "be administered coincident with an initial complete resection, with a 4 cm margin for the initial 5000 cGy."[27]

The use and extent of a margin in radiation therapy treatment planning is a topic of particular interest when comparing EBRT and SRS for malignant meningiomas. With SRS, Pollock et al. described tumor progression "away from the original irradiated tumor" in 30% of patients with atypical or anaplastic meningioma, occurring at a median of 15 months after SRS. Most (80%) were marginal, meaning "adjacent to the irradiated tumor."[113] Analyzing SRS and stereotactic EBRT for recurrent high-grade meningioma, Mattozo et al. found that 77% of recurrences were within the original resection cavity, and recommended that "the whole cavity receive radiation therapy," with an SRS boost to the recurrent nodule if desired. They suggested that EBRT to treat the entire tumor cavity after initial surgery may be appropriate to reduce the risk of any relapse.[75]

Indeed, the timing of radiation therapy appears to be an important factor. Some studies have shown modest benefit from irradiation in the recurrent setting,[27] but others have suggested little or no improvement from salvage radiation therapy.[75,122,138] Dziuk et al. reported that EBRT improved local control with malignant meningioma compared with surgery alone. Even in the recurrent group, 2-year PFS improved from 50% to 89% ($p = 0.002$) with EBRT, although it had no impact at 5 years.[27] Following initial resection, several investigators have found outcome improvement with radiation therapy (Table 7).[27,41,80,122]

Other radiation therapy factors may play important roles. As with atypical meningioma, higher radiation therapy doses appear to improve local tumor control for patients with malignant histology. Reviewing WHO Grade II and III patients, Milosevic found a 5-year cause-specific survival of 42% with at least 50 Gy versus 0% with less than 50 Gy.[80] With malignant lesions, Goldsmith et

TABLE 7. Eleven selected series reporting treatment outcomes for patients with anaplastic meningioma

Authors & Year	No. of Patients	FU* (study period)	Grading Scheme	Treatment Regimen	RT Dose*	Outcome	Comments
Jääskeläinen et al., 1986	11	Not reported (1953–1980)	Modified WHO 1979	Postop & salvage op alone or op + EBRT	Not reported	PFS: 5-yr 22%	Atypia & anaplasia developed in previously benign tumors w/o radiotherapy; 4 of 5 anaplastic tumors treated w/ op + EBRT recurred; EBRT doses not reported
Milosevic et al., 1996	42	Not reported (1966–1990)	Modified WHO 1979	Postop & salvage op + EBRT or salvage EBRT alone	EBRT 50 Gy	Cause-specific survival: 2-yr 63%, 5-yr 34%	Malignancy often diagnosed (60%) by brain invasion (60%), some hemangiopericytomas; negative predictive factors (cause-specific survival): age ≥58 yrs, EBRT before 1975, dose <50Gy; morbidity 3.4%; recommend immediate postop EBRT
Dziuk et al., 1998	38	29–39 mos (1984–1992)†	Russell & Rubinstein 1977	Initial & salvage op alone or w/ EBRT	EBRT 54 Gy	PFS: 2-yr 24%, 5-yr 25%	5-yr PFS: 39% after GTR, 0% STR; 28% GTR alone, 57% GTR+EBRT; intital postop EBRT improved 5-yr PFS from 15% to 80%, & salvage EBRT 2-yr PFS from 50% to 89%, but no benefit at 60 mos; 11 had hemangiopericytoma; no distant failures
Hug et al., 2000	16	59 mos (1973–1995)	WHO 1993	Postop & salvage photon + proton EBRT	EBRT photon + proton 58 CGE	Local control: 5-yr 52%, 8-yr 17%	Local control & overall survival improved w/ EBRT ≥60 Gy; 5- & 8-yr local control 100% & 33% w/ ≥60 CGE vs 0% w/ <60 CGE; late morbidity 9%
Mattozo et al., 2007	5	42 mos (1992–2004)	WHO 2000	Postop & salvage SRS or stereotactic EBRT	SRS 15.5 Gy, EBRT 49.3 Gy	PFS: 3-yr 0%	All patients had recurrent tumors; median SRS treatment vol 2.2 cm^3, median EBRT vol 21.3 cm^3; 77% of recurrences were w/in the original resection cavity
Kondziolka et al., 2008	29	48 mos (not reported)	Based upon "previous histopathology"	Postop & salvage single fraction SRS	SRS 14 Gy	Local control: 15 mos 17%, 5-yr 9%‡	Median tumor vol 7.4 cm^3; 5-yr cause-specific survival 22%‡; morbidity 7%, including symptomatic edema in 4%
Boskos et al., 2009	5	32 mos (1999–2006)	WHO 1993	Postop & salvage photon + proton EBRT; 1 patient hypofractionated protons alone	EBRT photon + proton 65 CGE	Mean relapse-free interval 23 mos	Median clinical target colume 151 cm^3; mean relapse-free interval for Grade II tumors 28.3 mos; overall survival & cause-specific survival improved w/ EBRT >60 Gy, & possibly further w/ >65 Gy; late morbidity in 1 patient, necrosis
Rosenberg et al., 2009	13	Not reported (1984–2006)	WHO 2007	Postop & salvage EBRT or SRS; 2 received systemic therapy (1 temozolomide, 1 immunotherapy)	EBRT 50–60 Gy, SRS 14–24 Gy, 5 Gy × 5	PFS: 1-yr 52%, 2-yr 17%, 3-yr 8.7%	Median time to recurrence 9.6 mos; median overall survival 2.5 yrs w/o vs 5.4 yrs w/ initial EBRT ($p = 0.13$); 5- & 8-yr overall survival 47.2% & 12.2%; radiation therapy morbidity 2 patients, both necrosis; recommend upfront radiation therapy
Sughrue et al., 2010	63	60 mos (not reported)	WHO 2007	Postop fractionated EBRT & some salvage brachytherapy or SRS, newly diagnosed & recurrent; 25% preop embolization	EBRT doses not reported	PFS: 2-yr 80%, 5-yr 57%, 10-yr 40%	Mean tumor vol 78 cm^3; 2-, 5-, & 10-yr overall survival 82%, 61%, & 40%; better survival w/ near-total resection than w/ GTR; significant neurological morbidity from attempted GTR

(continued)

TABLE 7. Eleven selected series reporting treatment outcomes for patients with anaplastic meningioma *(continued)*

Authors & Year	No. of Patients	FU* (study period)	Grading Scheme	Treatment Regimen	RT Dose*	Outcome	Comments
El-Khatib et al., 2011	7	60 mos (1990–2003)	WHO 2007	Postop & salvage single-fraction SRS, newly diagnosed & recurrent	SRS 14 Gy	PFS: 3-yr 57%, 5-yr 57%, 10-yr 43%	Median tumor vol 4.8 cm^3; 5-yr PFS 57%, 10-yr 43%; negative predictive factor (tumor control) age ≥50 yrs; morbidity 3.5%
Pollock et al., 2012	13	38 mos (1990–2008)	WHO 2000 & 2007	Postop & salvage single-fraction SRS, newly diagnosed & recurrent	SRS 15 Gy	Cause-specific survival: 1-yr 69%, 5-yr 27%	Median tumor vol 14.6 cm^3; negative predictive factors (cause-specific survival): prior EBRT & tumor vol > 14.6 cm^3; morbidity 26%; emphasize early SRS

* Mean or median.
† Follow-up listed by study groups, and varied accordingly.
‡ Actuarial percentage measured from graph.

al. reported a 5-year PFS rate of 63% using greater than 53 Gy versus 17% with no more than 53 Gy,[36] and Dziuk et al. recommend a total EBRT dose of 60 Gy, even after GTR.[27] More recent studies have specifically evaluated doses of this magnitude.

Using either photons or combined photons and protons, DeVries et al.[23] and Hug et al.[49] showed dramatic increases in local control and survival with a total dose exceeding 60 Gy. Hug et al., studying a mixed group of WHO Grade II and III meningiomas, identified a 5-year local control rate of 100% for patients receiving at least 60 CGE versus 0% with lower doses ($p = 0.0006$); the respective 8-year values were 33% and 0%. For the subgroup with malignant meningioma, improved local control corresponded with improved 5- and 8-year overall survival: 87% with at least 60 CGE and 15% with less than 60 CGE, respectively.[49] As mentioned with WHO Grade II tumors, some caution is prudent with dose escalation with these tumors. Katz and colleagues found no benefit from accelerated hyperfractionated radiation therapy, on occasion with an SRS boost, but did encounter unacceptable toxicity.[56]

Summary

Meningiomas are the most common primary intracranial tumors.[15] The majority are histologically benign (WHO Grade I) but even so can be clinically formidable. Due to a lack of prospective randomized trials, standardized treatment guidelines are difficult to formulate. Furthermore, uniformly applied guidelines have been difficult to achieve given the typical pattern of slow growth and given the availability of several management options. Granting these limitations, a growing body of largely retrospective evidence does permit inferences.

Small, incidental meningiomas can often be carefully observed, as recommended in the National Comprehensive Cancer Network guidelines. For most other patients, GTR remains the benchmark. However, complete tumor removal within the constraints of acceptable morbidity is not always achievable. Many meningiomas arise at or near critical neural or vascular structures or in sites with limited surgical access and can be very challenging for surgeons.[136] Based on these concerns and on other key features such as WHO grade, clinically significant subgroups of patients cannot be managed successfully by resection alone. When a GTR is not accomplished, postoperative radiation therapy, including SRS or EBRT, is an important consideration. In this setting, numerous studies have indicated improvements in local control, and some have shown significant cause-specific survival advantages as well. In spite of this, controversy remains regarding the most appropriate therapy after STR, particularly as to whether patients should be observed and treated at progression, or treated preemptively. Some patients do well for many years after STR alone, while others progress and develop larger symptomatic tumors more promptly.

Adding further controversy, there is increasing retrospective evidence in support of SRS or EBRT, not only in the adjuvant or salvage setting, but also as primary therapy. The relative efficacy of these approaches has not yet been tested in rigorously designed prospective clinical trials, but results with SRS and EBRT, at least for the ma-

jority of patients with known or presumed benign (WHO Grade I) meningiomas, have been remarkably similar, whether comparing them to each other or to reported results from surgery. Either SRS or EBRT can be recommended for many patients but not for all. EBRT is suitable for a broader range of patients, whereas excellent outcome with SRS has been realized among more distinct cohorts, taking neurovascular anatomy, location, edema risk, and tumor diameter or volume into careful account. At present, surgery retains a central role in management, acquires tissue for histological and molecular analysis, and promptly addresses rapidly progressive tumors or tumor-related symptoms. However, with this important caveat, excellent long-term results have been attained using SRS or EBRT administered either adjuvantly or primarily.

Many significant questions remain in the more common setting of benign meningioma, and with higher-grade meningioma these uncertainties are magnified. Current data support adjuvant radiation therapy for WHO Grade III meningiomas irrespective of the extent of resection, and for Grade II meningioma at least following STR. Considerable controversy persists for patients with a newly diagnosed and gross-totally resected WHO Grade II meningioma. At present they may be managed with postoperative radiation or with close observation. A randomized clinical trial has been designed to address this very question and is expected to open in the near future. This treatment decision is becoming a more clinically relevant question, as there have been notable increases in the incidence of WHO Grade II meningiomas with broader implementation of the current WHO grading criteria. The RTOG (no. 0539) and EORTC (no. 22042-22062) have recently completed accrual to Phase II clinical trials. From these studies there will likely be clinical outcome analyses to help integrate imaging, operative, central pathology, genotyping, immunohistochemical, microarray, and molecular (serum and urine) correlative findings.

A growing body of investigators are committed to the design and completion of prospective multicenter studies of meningioma and active in the above-mentioned studies and in the development of other trials. A companion article will evaluate the role of systemic therapies for patients with meningioma. Additionally, RANO is currently completing a manuscript proposing standardized end points and response criteria, providing investigators an opportunity to design trials and publish outcomes in a more uniform and consonant fashion.

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Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Vogelbaum, Rogers. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Vogelbaum.

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