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MENINGIOMAS:

Knowledge Base, Treatment Outcomes, and Uncertainties: A RANO Review

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Abstract

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. The current review summarizes the published literature regarding the treatment of newly diagnosed and recurrent meningioma, with an emphasis on outcomes stratified by World Health Organization (WHO) tumor grade. In particular this review focuses on patient outcomes following treatment (either adjuvant or at recurrence) with surgery or radiation therapy inclusive of radiosurgery and fractionated irradiation.

Phase II trials for patients with meningioma have recently completed accrual within the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) 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 radiotherapy. Successful completion of future studies will require a multidisciplinary effort, dissemination of the current knowledge base, improved implementation of WHO grading criteria,

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standardization of response criteria and other outcome endpoints, 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 manuscript on systemic therapies for meningioma, and a separate article proposing standardized endpoint and response criteria for meningioma.

Keywords

Meningioma; Outcomes; Surgery; Radiotherapy

Introduction

Harvey Cushing first used the term "meningioma" in a 1922 publication describing tumors that originate from the meningeal, i.e. dural, coverings of the brain and spinal cord.[20] 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 understanding of the molecular genetics of these tumors.

With reference to molecular genetics, meningiomas occur with greater frequency in genetic conditions such as type 2 neurofibromatosis (NF2),[108,109] or multiple endocrine neoplasia type 1 (MEN1).[4] Nearly all NF2-associated meningiomas, and many sporadic meningiomas, have mutations of the NF2 gene.[121] Nevertheless, phenotypic NF2 accounts for only a small minority. MEN1 has also been reported to carry an increased risk for meningioma, although with less likelihood of aberration at the NF2 gene locus.[4] However, there is no clear documentation that NF2 or MEN1 associated meningiomas behave more aggressively than their sporadic counterparts.

Incidental, asymptomatic, radiographically presumed meningiomas appear to behave less aggressively,[12,145] may be observed, and treatment withheld until symptoms develop, sustained growth occurs, or concerns of encroachment on sensitive structures arise.[94] The focus of this manuscript 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 their results have been described in other papers.[12,46,91,92,101,145] 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 2 [atypical] or Grade 3 [malignant] meningioma). For patients undergoing definitive therapy, complete surgical resection has been the standard for meningioma, however, 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 the relationship of tumor to eloquent anatomy. The potential for recurrence, whether following subtotal resection (STR) or gross total resection (GTR), is well recognized in the literature.[19,87,118,136,138,148] Limitations associated with an initial treatment strategy of surgical resection alone are even more apparent for patients with recurrent or high-grade meningioma. [2,78] The current WHO criteria[110] 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 upon the extent of resection has been questioned in the MRI era.[19,100,144,146] In particular the surgeon's observations at the time of surgery are critical toward 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 radiotherapy (RT), including single session stereotactic radiosurgery (SRS), hypofractionated stereotactic radiotherapy (FSRT), and conventionally fractionated external beam radiotherapy (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 RT 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 histopathologic or molecular measures. Recognizing that these studies are largely retrospective or single arm in design, as will be reviewed herewith, they have suggested improved tumor control compared to surgery alone or to observation. At present the most appropriate patients, tumor target volumes, radiation dose, 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 progression risk than their initially diagnosed WHO grade I counterparts.[107] 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. Pharmacologic 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.[37,44,83,107] 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 upon prior grading schemes. This renders comparisons among many published difficult and tenuous.

It is also important to recognize that the reported incidence of all grades of meningioma has varied substantially over time and by the method of meningioma identification, from 1 to 8.4 per 100,000.[79] Considering both microscopically confirmed and presumed tumors, a recent analysis reported an incidence of 3 to 3.5 per 100,000.[50] Adjusting for increases in population in the United States (USA), approximately 150,000 persons are currently diagnosed with meningioma.[15,22] Outcomes may vary according to histologic, genetic, tumor size and location, presenting clinical characteristics, and even by the method of identification.

Recognition of the limitations of existing methods to evaluate outcomes of neuro-oncology 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 neuro-oncologists, neurosurgeons, radiation oncologists, neuro-radiologists, 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 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 neuro-oncology, 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 outcomes measures. [69,70,120,153,154,157,160]

Appreciating these important qualifications, this overview will examine published treatment outcomes, underscore deficiencies in our meningioma-related knowledge base, provide a foundation for response assessment (for which a future RANO publication is in progress) and suggest opportunities for future research. This manuscript 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 meningioma 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 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, histologic grade, and outcome measures. For surgery patients, the extent of resection was collected, and for patients receiving radiation therapy or radiosurgery, dose and, when available, target volume definitions were recorded. Applicable outcome measures were recorded, along with their respective time points. The most consistently reported measure was progression-free survival at 5 years, and when possible this was used as a unifying endpoint.

Results

WHO Grade I (Benign) Meningioma

Meningioma has long been recognized as the most common non-glial intracranial tumor.[10] Recent data reveal that they are, in fact, the most frequently reported primary intracranial neoplasm,[15] accounting for 33.8% of all such tumors.[11] The majority of meningiomas are benign. With more uniform adoption of the current WHO 2007 standards, approximately 65% to 80% are grade I (see Figure 1).[107,162]

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 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.[134] The completeness of surgical removal has consistently been identified as an important prognostic feature, [19,23,115,138] and the majority of centers continue to use Simpson’s criteria.

Sughrue challenged the applicability of the Simpson classification in the present era. With 373 WHO grade I meningioma patients followed for a median of 3.7 years, they found no significant difference in 5-year progression-free survival (PFS) following Simpson grade I through IV resections, with respective 5-year PFS results of 95%, 85%, 88%, and 81% (p=ns).[144,146] Similar findings were reported previously by Condra,[19] and more recently by Oya.[100] These studies, while identifying no difference in local control after Simpson grade I-III resections, did reveal shorter PFS following Simpson grade IV surgery.[19,100] A large series by Hasseleid of 391 patients with convexity meningioma, studied 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 grade 4+5[47] serving in support of the continued applicablility of Simpson’s crieteria.

GTR (Simpson I-III) 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 ,[87,115] and in over 95% of convexity meningiomas.[90] For benign meningioma, GTR is considered definitive therapy.[19,87,115,138] However, with extended follow-up, recurrences in this setting are not infrequent.[1,19,87,136,138,148] 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.[136]

STR (e.g. Simpson IV-V) 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 37–47% at 5 years, to 55 to 63% at 10 years, and to 70 to 91% at 15 years. Condra also found that STR impacted cause-specific survival. Their patients with STR alone experienced a 15-year cause-specific survival of 51%, significantly inferior to 88% after GTR, and 86% after STR+RT (p=.0003).[19] In a recent evaluation of clinical and molecular prognostic features of meningioma, Jensen reported that STR was associated with both poorer progression-free and overall survival.[57] In spite of these reports, observation remains commonplace following STR. A Mayo Clinic series detailed 581 patients, 116 (20%) of whom had STR. Only 10 (9%) of these patients received adjuvant radiation therapy.[138]

Patients with WHO Grade I meningioma have lengthy survival expectations (Figure 1), and hence 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[136] (Table 3). Moreover, recurrent meningioma exhibits a several-fold increased risk of progression and a shorter interval to progression than newly diagnosed tumors.[19,86,87,148] Miralbell reported an 8-year PFS of 11% in recurrent tumor with surgery alone, compared to a rate of 78% following a combination of surgery and adjuvant EBRT.[86] Taylor found a 5-year PFS of 30% with surgery alone for recurrent meningioma, 88% with surgery and EBRT. They also reported 5-year overall survival of 45% and 90%, respectively.[148] These data support the need for prospective clinical investigation of methods to prevent recurrence, and provide impetus for research into clinical, imaging, histopathologic, and molecular predictors of response to treatment and to tumor progression.

WHO Grade I - Radiation Therapy

Multiple retrospective studies have demonstrated that various forms of radiation therapy (RT), including SRS and EBRT can provide improved and durable local control in selected patients with meningioma. RT has most commonly been utilized as an adjunct to surgery following STR, as treatment for recurrence, or for tumors of high-grade histology. Additionally, as shown in Table 4 and Table 5, many studies document excellent local control with SRS or EBRT as a primary modality. In these studies, RT was used predominantly for tumors in difficult to surgically access locations such as the optic nerve sheath or cavernous sinus, for patients regarded as inoperable for medical reasons, or for those who chose primary RT over surgery.[32,66,67,71,76,80,104,116,129] These studies show that RT achieved long-term local control in 68% to 100% of WHO grade I or presumed grade I meningioma at 5 to 10 years, including patients treated post-operatively, primarily, or following recurrence. Results varied somewhat by treatment era, tumor size and location, and clinical setting.

Stereotactic Radiosurgery (SRS)—SRS was developed more recently than fractionated EBRT, and over the past 2 to 3 decades has been used with increasing frequency. It has been used after STR or for recurrence ,[61,65,139] and as a definitive primary treatment .[32,116,117,118] Table 4 includes 35 studies of SRS, and demonstrates that local control was achieved in the majority of patients at 5 to 10 years.

SRS is considered most effective for patients with small meningiomas, typically those that are less than 3 cm in diameter or 10cc 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 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.[33] Stafford reported no reduction in local control at 5 years with tumor margin doses of less than 16 Gy as compared to greater than or equal to 16 Gy.[139] Similarly, Kondziolka reported no improvement with marginal doses greater than 15 Gy versus less than 15 Gy.[63]

With respect to tumor size, DiBiase reported a 91.9% 5-year disease-free survival for patients with meningioma less than 10 cc (equivalent diameter 2.7 cm), as opposed to 68% for larger tumors.[25] Kondziolka reported excellent outcomes with SRS for meningioma up to a diameter of 3.0 cm or a volume of 7.5 cc.[63] Likewise, other authors have found excellent local control (10-year 99.4%), and fewer radiation-related complications with smaller meningiomas, with complications in 4.8% of patients with tumors in the smallest quartile (<3.2cc) but in 22.6% in the largest quartile (>9.6cc).[116,117]

Pollock reported 188 benign or presumed benign meningioma patients treated with either surgery or SRS alone. With median follow-up of 64 months, 7-year PFS with SRS and Simpson grade I surgery were equivalent 95% and 96%, respectively. However, SRS resulted in superior tumor control when compared to less extensive surgery. The authors concluded that SRS should be a primary option when Simpson grade I resection is unlikely.[118] In an updated analysis of primary SRS, Pollock found 10-year local control was 99.4%. They used 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.[116,117]

SRS for meningioma has traditionally been single session. However, reports of multi-session SRS are emerging.[18,34,72,76,89,150] 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 non-basal/parasagittal or large meningiomas. In one of these reports, Unger reported on 173 patients and found that symptomatic edema was significantly less common following multifraction (typically 25 Gy in 5 fractions) SRS than single session (median 15 Gy) SRS. The respective 2-year actuarial risks were 3.2% and 12.5%. Single session SRS and tumor volume >4.9cc were significant predictors of symptomatic edema.[150]

Girvigian published on 30 convexity or parasagittal meningioma patients, 14 treated with single fraction and 16 with multifraction SRS. Multifraction treatment was typically 25 Gy in 5 fractions, and was used for larger tumors. Symptomatic edema occurred in 43% following single fraction, as opposed to 6.3% (1 patient) after multi-fraction SRS, and this patient had pre-treatment edema. Single doses of more than 14 Gy and larger tumor volume were predictors of edema.[34]

Columbo 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 8cc in volume who were treated with multi-fraction SRS (14–25 Gy in 2–5 fractions). For the entire cohort, 5-year PFS was 93%. They 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.[18]

Fractionated External Beam Radiation Therapy (EBRT)—Historically meningioma has been considered resistant to irradiation, probably due to infrequent documentation of tumor regression following the use of EBRT. EBRT was also felt to produce considerable side effects, to potentiate malignant degeneration, and indeed to cause meningiomas.[60,87,126,143] These concerns likely remain an issue today, and as a consequence many patients with inoperable or subtotally resected are managed by observation.[3,138] A recent publication by Sughrue reported the outcomes of 373 patients with a newly diagnosed WHO grade I meningioma -- the preponderance located at the skull base -- treated with surgery alone. Simpson resection grades were I in 88 patients (23.6%), II in 114 (30.6%), III in 57 (15.3%), and IV in 114 (30.6%),[144,146] 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 higher tumor grade), reliable estimates are difficult to ascertain. Dedifferentiation has not been definitively linked to RT, and as well is the natural history of a subgroup of recurrent or progressive meningioma.[55,96] To establish radiation-induced malignant transformation, detailed histology prior to irradiation would be indispensable. Moreover, irradiation is often employed only after imaging-confirmed regrowth, without additional histology. Thus whether dedifferentiation results from irradiation or as a result of natural cellular evolution cannot be readily determined.[96] 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, who reported as actuarial risk of 0.53% at 5 years, and 8.18% at 25 years.[143] This risk appears to be considerably smaller with modern, highly conformal therapy. Minniti reported 426 pituitary adenoma patients treated with surgery and small field EBRT, and followed for 5,749 person-years. The risk of second brain tumor at 20 years was 2.4%. Of the 11 second tumors 5 were meningioma.[85] With even smaller field treatment using SRS, and with over 9000 patients, Niranjan estimated a second tumor risk of less than 1 per 1000.[96] This is smaller than the published series using larger field non-conformal 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 found 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 meningioma (ONSM). 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 plus EBRT.[93,104,149] Moreover, patients with ONSM commonly experience improved visual acuity following use of EBRT.[93,104,149]

Primary EBRT for intracranial meningioma not involving the optic nerve sheath has also resulted in excellent local control, clinical improvement, and low rates of toxicity (Table 5). Tanzler 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%.[147]

Technical improvements in the delivery of EBRT have favorably impacted 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 and Milosevic each substantiated improvements in local control with modern imaging.[36,37,83] Goldsmith found that, with immobilization techniques and with CT or MRI based planning, 10-year PFS improved from 77% to 98% (p=0.002).[36,37]

Recommended EBRT doses for benign meningiomas are generally 50 to 55 Gy with fraction sizes of 1.8 to 2.0 Gy,[19,36] but a dose-response relationship has not been unequivocally established. Goldsmith reported that doses above 52 Gy resulted in improved 10-year local control, but this effect was not substantiated on multivariate analysis.[37] Winkler found no clear dose response from 36–79.5 Gy (1.5 to 2.0 Gy per day).[163] 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.[93,132] Figure 2 displays pre-operative and post-operative MRIs 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. Table 5 summarizes data from 35 studies with 4389 patients. Less than 0.5% of patients are 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 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.[130] Tanzler studied 146 patients treated with EBRT and two (1.4%) developed edema.[147] It appears that edema is a less likely a 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, and represents an avenue for further research.

WHO Grade II (Atypical) Meningioma

Although grade II meningiomas were for decades 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 meningioma.[15,105,107,162] 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 being implemented, and to define the rates of inter-observer and inter-institutional concordance in diagnosis. These investigations are crucial since, as shown in Figure 1, atypical meningioma carries a 7 to 8 fold increased risk of recurrence at 5 years, and an increased rate of mortality compared to WHO grade 1 meningioma.[107]

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 pathologic criteria, which underreported the incidence of atypical meningioma. Both the recently completed RTOG and EORTC prospective trials included central review of pathology, and analysis of their pathologic material is eagerly awaited. There is general agreement, but not consensus, that subtotal resection 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.[77,133] 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 post-operative radiation therapy.[39] 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% of centers (47 of 56) recommended surgery alone for initially diagnosed, gross totally resected WHO grade II meningioma,[133] similar to the United Kingdom where 80% made the same recommendation.[77] A number of other reports have suggested that GTR alone is sufficient for these patients.[39,73,75,102,105] Jaaskelainen reported a 38% 5-year local recurrence after GTR, and did not find that adjuvant RT was of utility.[55] 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 RT doses that were, as will be discussed subsequently, likely too low to be effective.

Employing WHO 2000/2007 criteria and higher EBRT doses, Aghi analyzed 108 patients with atypical meningioma. Following Simpson grade I surgery alone, the 5-year local recurrence was 50%.[2] A more recent report by Komotar reviewed outcomes among 45 patients, each with a gross totally resected atypical meningioma. GTR was defined as Simpson grade I or II, confirmed by post-operative MRI. Thirty-two of their 45 patients (71%) were treated initially with surgery alone, and experienced a 5-year actuarial risk of recurrence of 55%.[62]

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 found that neither the extent of salvage resection nor the use of RT was predictive of outcome for patients with recurrent grade II meningioma.[75] Aghi reported a 10-year disease-specific survival after first recurrence of 69%.[2] With a median follow-up of 44.1 months, Komotar noted crude overall survival of 69.2% following first recurrence, very similar to Aghi,[2] and concluded that recurrences resulted in shortened overall survival, as well as additional treatment burden.[62]

Radiation Therapy

Various forms of RT have been used for grade II meningioma following STR, including SRS[5,58,135,139] and EBRT.[2,8,17,19,52,83] Even following GTR, many have advocated RT for these patients,[2,19,44,51,52,103,163] but others recommend observation.[39,75,105] Irradiation is also commonly employed as a primary modality for some meningioma, but as there was no pathological confirmation it is unclear how many were, in reality, WHO grade II tumors. The determination of grade requires tissue confirmation, and there is very limited data on primary RT after biopsy alone.

Achieving local control for patients with atypical meningioma is an important endpoint with RT, and appears to be paramount. As aforementioned, Aghi reported a 69% 10-year disease-specific survival after first recurrence.[2] Skeie found that 6 of 7 recurrent patients died of disease at a mean 25 months after regrowth.[135] Stafford 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.[139]

Stereotactic Radiosurgery (SRS)—Reports of SRS for grade II meningioma are, with near exclusivity, in the STR or recurrent settings, mostly the latter. Table 6 summarizes 8 series. 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 reported that 5-year PFS for lesions treated below 20 Gy was 29.4%, as compared to 68% for those receiving 20 Gy (p=.0139).[58] However, Stafford 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.[139]

Attia, studying dose and conformality index (CI = 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, median time to recurrence 25 months. When CI was considered, margin dose was not predictive of local control.[5] The mean CI was 1.7 in the patients who recurred, and 4.6 in those who did not (p=.038). This raises the possibility that higher doses in some studies[58] might in part be a proxy for a larger CI.

This finding is supported by other studies showing that atypical meningioma may recur outside of the SRS target, yet inside the resection bed. Huffmann treated 15 patients to a median 16 Gy. At 18 to 36 months, 9 were progression-free, for a crude local control of 60%. Six (40%) progressed, 1 (17%) in field, but all within the surgical approach or resection bed.[51] Choi reviewed 25 grade II patients, median marginal dose 22 Gy (range 16–30 Gy) in 1–4 fractions (median 1). Recurrence was identified in nine, 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 of target definition.

Timing of treatment may also influence outcome. Choi showed improved local control with immediate (within 6 months of surgery) post-operative SRS as opposed to SRS at recurrence or progression.[13] Harris, defining “late” as after radiographic progression and “early” as after craniotomy without imaging evidence of progression, found a median time to neurologic progression of 15 months after “late” SRS, versus 61 months with “early” treatment.[44]

Multi-session SRS has also been employed for grade II meningioma, often for larger or critically located tumors, involving for instance the anterior optic apparatus, or the sagittal sinus where edema may occur after single fraction SRS.[18,34,150] Local control results have been essentially equivalent to single fraction therapy,[18] possibly with a lower risk of side effects.[18,34,150] Vernimmen reported multi-fraction SRS using protons. With a mean follow-up of 40 months, 88% remained under control. With the multifraction approach, they were able to treat larger tumors, up to 63cc.[156] Presently, multi-fraction SRS data specific to atypical meningioma is limited. Its role and proper dose-volume constraints remain important research questions.

Fractionated External Beam Radiation Therapy (EBRT)—Several investigators have reviewed EBRT for atypical meningioma, some recommending EBRT irrespective of resection extent,[19,52,163] but others have questioned its benefit. Goyal reported local control of 87% at 5 and 10 years among 22 patients. EBRT was used in 8, with a median dose 54 Gy, but did not significantly impact outcome.[39] Hoffmann identified 10 grade II patients. The post-operative 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.[50]

Aghi published an analysis of 108 patients with atypical meningioma and Simpson grade 1 resection. One hundred (93%) had surgery alone, and 8 (7%) surgery + 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 + EBRT. This difference did not reach statistical significance (p=0.1), perhaps owing to the relatively small number of events. They 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% had died as a result of recurrence.[2]

Similarly, Komotar reported on 45 patients with atypical meningioma and with a Simpson grade I or II resection. Thirty-two had GTR alone and 13 GTR + EBRT, median 59.4 Gy, to a target described as the tumor cavity plus a 0.5 to 1.0 cm margin. After surgery alone, 13 patients (41%) recurred at a median 19 months. After GTR + EBRT 1 patient (8%) recurred at 52.5 months. Following GTR alone versus GTR + EBRT, the respective 6-year actuarial recurrence risks were 65% versus 20% (p=0.085).[62] Other recent analyses have supported EBRT in this setting. Park reported 5-year PFS rates of 46.4% with GTR alone, 77.9% with GTR + EBRT, 0% with STR alone, and 55.6% for STR + EBRT. PFS was improved by EBRT, regardless of resection extent.[103]

Others have reached different conclusions. Mair suggested EBRT was not appropriate following GTR, and advised SRS rather than EBRT following STR.[75] In spite of this contention, their report did confirm that EBRT improved PFS when comparing surgery alone to surgery + EBRT. Four-year PFS rates were respectively, 13% following surgery alone versus 72% with surgery and EBRT (p=.043). These results were not stratified by extent of resection, and they used a relatively low mean EBRT dose of 51.8 Gy in 28 fractions.[75] Hardesty 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 I or II, was achieved in 58% of patients. Appreciating the lack of statistical significance it is notable that no patient is this study treated with a GTR and post-operative radiation therapy experienced recurrence, with actuarial data extending 7 to 9 years.[43] In this series, the number and length of follow-up of patients managed with GTR and radiation therapy was limited. Their median RT dose, 54 Gy with 1.8 to 2.0 Gy fractions, as discussed below, may be lower than optimal, but in spite of these, there were no recurrences in patients treated with GTR and radiation therapy.

A SEER-based analysis by Stessin *et al* reviewed 657 patients treated for a non-benign meningioma from 1988–2007.[141] Two hundred and 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 found not 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 irradiation, possibly reflecting a treatment selection bias for patients with poor overall prognosis. Stessin did not analyze local control, and did not factor in EBRT doses or target definition parameters.[141]

This may be of critical importance since higher EBRT doses appear to improve outcome for grade II meningioma. Park found an improved PFS using a mean dose of 61.2 Gy.[103] Aghi observed no local recurrences with 59.4 to 61.2 Gy,[2] and Komotar had numerically better outcomes with a median EBRT dose of 59.4 Gy. The RTOG trial (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 current EORTC trial (22042–26042) employs 60 Gy following a GTR, and adds a 10 Gy boost after STR. This trial will ultimately provide important guidance regarding dose-escalation for atypical meningioma.

Studies of proton radiotherapy further illuminate questions of dose. Hug 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 CGE (Cobalt-Gray-Equivalent). Local control was significantly improved with doses > 60 CGE, with 5-year local control 90% with > 60 CGE, and 0% < 60 CGE. They 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.[52] Boskos published outcomes with 24 high-grade meningioma patients, typically treated following STR. Nineteen (79%) were WHO grade II. Cause-specific survival at 5 years was 80% with > 60 Gy versus 24% with < 60 Gy (p=0.01). There was a trend toward further improvement with doses above 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 for high-grade meningioma, but caution with dose escalation is warranted. Using accelerated hyperfractionated EBRT with or without an SRS boost, Katz found a high rate of complications with no improvement in tumor control.[59] Future research of RT 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 USA.[50] 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 meningioma. In studies used to determine WHO grading, median overall survival has been less than 2 to 3 years (Figure 1).[111,112] There is little discrepancy in recommendations for aggressive treatment, typically including surgery and radiation therapy (RT), but regarding the required extent of surgery, the preferred type of RT, 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, as well as establishing a diagnosis. As is the case with lower grade meningioma, recurrence corresponds to the extent of tumor removal.[28,39,102,111] However, the success of surgery alone has not been satisfactory. Jaaskelainen reported a 5-year recurrence rate of 78% following GTR for patients with anaplastic meningioma, less than half of whom received any adjuvant therapy.[55] Among patients with malignant histology treated with surgery alone, Dzuik encountered a 5-year PFS of 28% after GTR, and 0% after STR.[28] Most investigators now recommend adjuvant therapy.[29,116,144]

When a clear plane between the tumor and surrounding normal structures can be identified, GTR remains the goal of surgery for anaplastic meningioma.[144] Sughrue recently analyzed resection extent for WHO grade III patients. All patients were also referred for post-operative EBRT. They found that heroic surgical efforts did not improve survival, and even compromised neurologic outcome. Specifically, they found improved overall survival with near total resection (NTR) as opposed to GTR. NTR implied >90% tumor removal.[144]

Surgery appears of benefit at recurrence as well. Correcting for other prognostic factors, Sughrue found a survival benefit from repeat operation, with median survivals of 53 months with salvage surgery versus 25 months without (p=.02). All patients received EBRT, and some also received radiosurgery or brachytherapy. As with their patients in the *de novo* setting, NTR resulted in superior median survival to GTR, 77 versus 42 months (p=.005).[144] In contrast, other investigators have found that the mode of salvage therapy for WHO grade III patients did not significantly affect time to subsequent progression.[127]

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.[19,28,83,127,136] 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 histologic grading standards employed, the extent and type of follow-up, and the timing of irradiation.

Stereotactic Radiosurgery (SRS)—Some authors have argued that SRS is not indicated for malignant meningioma,[88] however, several studies have reported outcomes with SRS (Table 7). Kondziolka treated 29 WHO grade III patients with post-operative SRS, mean margin dose 14 Gy, and found PFS rates of 17% at 15 months, and 9% (extrapolated from graph) at 5 years.[65] 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.[64]

El-Khatib reported 7 patients with WHO grade III meningioma, using a 14 Gy margin dose. They found considerably higher rates of PFS, 57% at 3-years and 43% at 10 years. This study employed similar tumor margin doses to Kondziolka. The mean target volumes were modestly smaller in the El-Khatib study (4.8 versus 7.4 cc). 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 used the WHO 2007 criteria. These differences in diagnostic criteria may play a role in accounting for the differences in results.

Pollock recently published an experience with 50 WHO grade II or III patients, treated in both the *de novo* and salvage settings. Thirteen had anaplastic meningioma. Their median treatment volume was larger at 14.6 cc, and median dose modestly higher at 15 Gy. Disease-specific survival at 1 and 5 years for the WHO grade III patients was 69% and 27%. They 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 40%. For patients who had failed prior EBRT, PFS was lower, 19% at 3 years.[117]

Fractionated External Beam Radiation Therapy (EBRT)—The early experiences of Milosevic[83] and Dziuk[28] 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. Melosevic found that patients who received < 50 Gy experienced inferior cause-specific survival, as did those treated before 1975 (i.e. before CT based planning).[83] Dziuk found that EBRT improved 5-year PFS from 50% to 80% compared to 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."[28]

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 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.[116] Analyzing SRS and stereotactic EBRT for recurrent high-grade meningioma, Mattozo 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.[78]

Indeed the timing of RT appears to be an important factor. Some studies have shown modest benefit from irradiation in the recurrent setting,[28] but others have suggested little or no improvement from salvage RT.[78,127,144] Dziuk reported that EBRT improved local control with malignant meningioma over surgery alone. Even in the recurrent group, 2-year PFS improved from 50% to 89% ($p=.002$) with EBRT, although it had no impact at 5-years.[28] Following initial resection, several investigators have found outcome improvement with RT (Table 7).[28,44,83,127]

Other RT factors may play important roles. As with atypical meningioma, higher RT 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 ≥50 Gy versus 0% with <50 Gy.[83] With malignant lesions, Goldsmith reported a 5-year PFS of 63% using >53 Gy versus 17% with ≤ 53 Gy,[37] and Dziuk recommend a total EBRT dose of 60 Gy, even after GTR.[28] More recent studies have specifically evaluated doses of this magnitude.

Using either photons or combined photons and protons, DeVries[24] and Hug[52] showed dramatic increases in local control and survival with a total dose exceeding 60 Gy. Hug, studying a mixed group of WHO grade II and III meningiomas, identified 5-year local control of 100% for patients receiving ≥60 CGE versus 0% with lower doses (p=.0006). The respective 8-year figures were 33% and 0%. For the subgroup with malignant meningioma, improved local control corresponded with improved 5 and 8 year overall survival: 87% with ≥60 CGE and 15% with <60 CGE.[52] As mentioned with WHO grade II tumors, some caution is prudent with dose escalation. Katz found no benefit from accelerated hyperfractionated RT, on occasion with an SRS boost, but did encounter unacceptable toxicity.[59]

Summary

Meningiomas are the most common primary intracranial tumor.[15] The majority are histologically benign (WHO grade I), but even if benign can be clinically formidable. Owing 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 NCCN guidelines. For most other patients, gross total resection (GTR) remains the benchmark. However, complete 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.[142] Based upon these concerns and upon 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 RT, including SRS or EBRT, are important considerations. In this setting, numerous studies indicated improvements in local control. Some have shown significant cause-specific survival advantages as well. In spite of this, there remains controversy regarding most appropriate therapy after subtotal resection (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 majority 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 histologic 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 irradiation for WHO grade III meningioma irrespective of resection extent, and for grade II meningioma at least following STR. Considerable controversy persists for patients with an newly diagnosed and gross totally resected WHO grade II meningioma. At present they may be managed with post-operative irradiation 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 is becoming a more clinically relevant question. There have been notable increases in the incidence of WHO grade II meningioma with broader implementation of the current WHO grading criteria. The RTOG (0539) and EORTC (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 is committed to the design and completion of prospective multicenter studies of meningioma, and is 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 endpoints and response criteria, providing investigators an opportunity to design trials and publish outcomes in a more uniform and consonant fashion.

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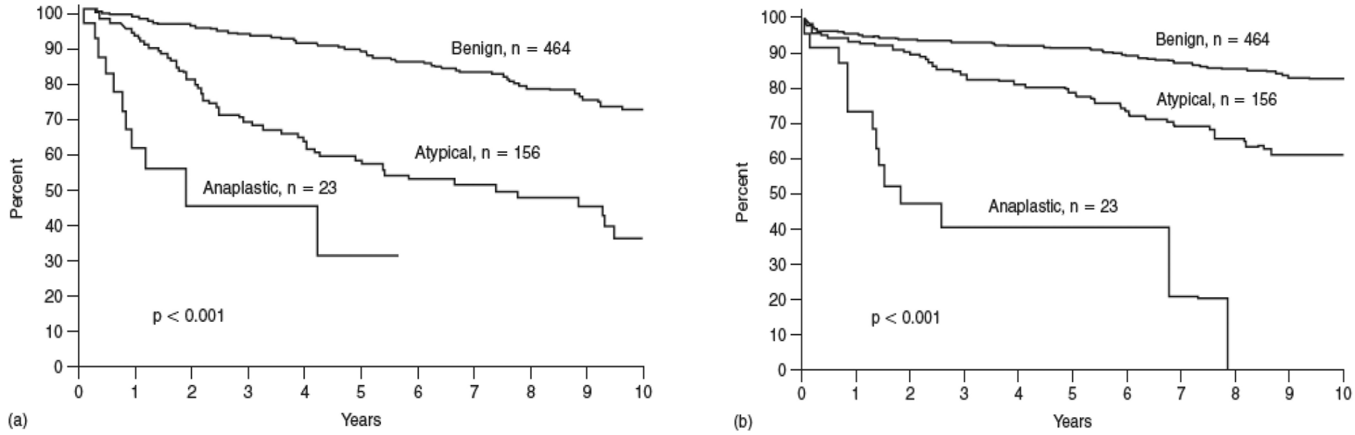

Figure 1.

Recurrence-free (a) and overall (b) survival 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%) grade II, and 23 (3.5%) grade III].[100]

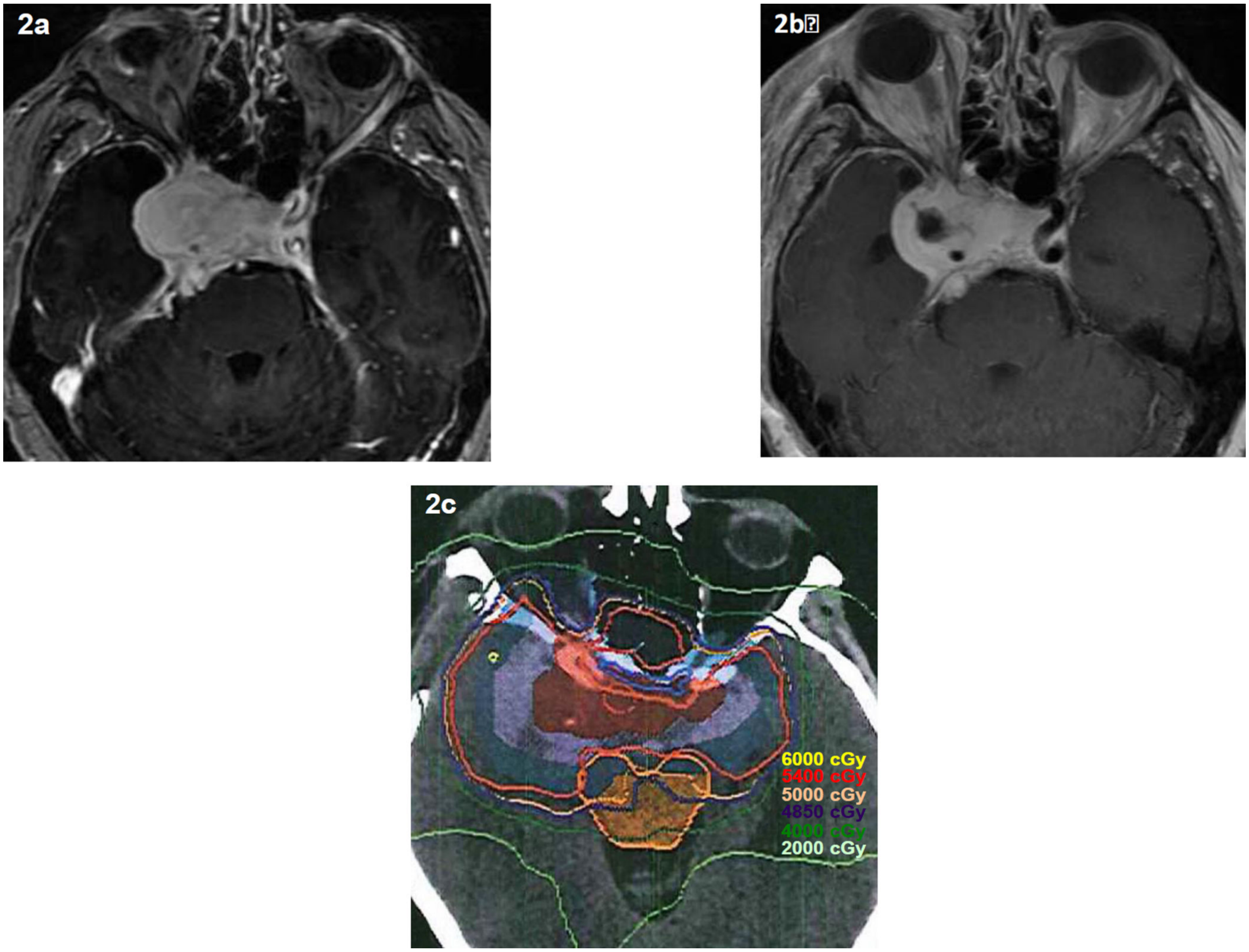

Figure 2.

Pre-operative (2a) and post-operative (2b) MRIs as well as the dosimetry plan CT (2c) for EBRT on a patient with a subtotally resected WHO grade I meningioma. The prescription dose is 5400 cGy in 30 fractions (180 cGy per fraction). Courtesy of Heyoung McBride, MD and Terry Thomas, MS, Barrow Neurological Institute, Phoenix, AZ.

Table 1

Simpson grades of resection, as derived from a series of 265 patients. [Simpson 1957].

Extent of Resection Simpson's Grade		
Resection Grade	**Definition**	**Recurrence (%)**
1	GTR of tumor, dural attachments and abnormal bone	9%
2	GTR of tumor, coagulation of dural attachments	19%
3	GTR of tumor without 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)	-

GTR: gross total resection

Table 2

Five single institution series with prolonged follow-up, documenting rates of recurrence following gross total resection alone.

Local Recurrence After Gross Total Resection Alone						
				Local Recurrence Rate		
Author	**Institution**	**Year**	**n**	**5-year**	**10-year**	**15-year**
Mirimanoff	MGH	1985	145	7%	20%	32%
Taylor	U of Florida	1988	90	13%*	25%*	33%*
Condra	U of Florida	1997	175	7%	20%	24%
Stafford	Mayo Clinic	1998	465	12%	25%	-
Soyuer	MD Anderson	2004	48	23%	39%	60%*
		Total:	**923**	**7–23%**	**20–39%**	**24–60%**

n: number of patients

MGH: Massachusetts General Hospital; U of Florida: University of Florida

* data extracted from graph

Table 3

Seven single institution series with prolonged follow-up, assessing rates of recurrence following sub-total resection alone.

Local Progression After Sub-Total Resection Alone						
				Local Progression Rate		
Author	**Institution**	**Year**	**n**	**5-year**	**10-year**	**15-year**
Wara	UCSF	1975	58	47%	62%	-
Barbaro	UCSF	1987	30	40%*	100%*	-
Mirimanoff	MGH	1985	80	37%	55%	91%
Condra	U of Florida	1997	55	47%	60%	70%
Mirabell	MGH	1992	79	40%	52%§	-
Stafford	Mayo Clinic	1998	116	39%	61%	-
Soyuer	MD Anderson	2004	32	62%	82%*	87%*
		Total:	**450**	**37–62%**	**52–100%**	**70–91%**

n: number of patients

UCSF: University of California San Francisco; MGH: Massachusetts General Hospital;

U of Florida: University of Florida

* data extracted from graph

§ 8-year progression

Table 4

Thirty-five studies of stereotactic radiosurgery, largely for WHO grade I or presumed grade I meningiomas

						Stereotactic Radiosurgery					
First Author	Year	n	Technique	Location	Mean FU (months)	Mean/ Median Dose (Gy)	5yr/10yr PFS (%)	Clinical Improvement (%)	Tumor Regression (%)	Complication (%)	Mean/Median Tumor Vol (cc)
Roche	2000	80	GKRS	Cav Sinus	30.5	14	92.8 / --	27	31	4	5.8
Shin	2001	40	GKRS	Cav Sinus	42	18	91.3 / 91.3	--	37.5	2.5	4.3
Stafford	2001	190	GKRS	All	47	16	93 / --	8	56	13	8.2
Eustacchio	2002	121	GKRS	Skull Base	72	13	99 / --	44.6	60	5	6.8
Lee	2002	159	GKRS	Cav Sinus	35	13	93 / 93	29	34	5	6.5
Nicolato	2002	111	GKRS	Cav Sinus	48.2	14.8	96 / --	66	61	4.5	8.1
Spiegelmann	2002	42	LINAC	Cav Sinus	36	14	97.5 / --	22	60	16.7	8.2
Flickinger	2003	219	GKRS	All	29	14	93.2 / --	--	--	8.8	5
Iwai	2003	42	GKRS	Cav Sinus	49	11	92 / --	29	59.5	4.7	12.4
Pollock	2003	62	GKRS	All	64	17.7	95 / --	13	--	10	7.4
Roche	2003	32	GKRS	Petroclival	56	13	100 / --	58	12.5	9.3	--
Chuang	2004	43	LINAC	Skull Base	74.5	17	89.7 / --	16	37	11	4.5
DiBiase	2004	137	GKRS	All	54	14	86.2 / --	--	28	8.3	4.5
Kreil	2005	200	GKRS	Skull Base	94	12	98.5 / 97	41.5	56.5	2.5	6.5
Pollock	2005	49	GKRS	Cav Sinus	58	15.9	100 / --	26	59	14	10.2
Zachenhofer	2006	33	GKRS	Skull Base	103	17	94 / --	44	36	12	--
Davidson	2007	36	GKRS	Skull Base	81	16	100 / 94.7	44	14	2.8	4.1
Hasegawa	2007	115	GKRS	Cav Sinus	62	13	94 / 92	46	--	12	13.8
Kollova	2007	331	GKRS	All	68	12.5	98 / --	62	70	10	6.3
Han	2008	63	GKRS	Skull Base	77	12.7	90.2 / --	45	44	17	6.3
Iwai	2008	125	GKRS	Skull Base	86	12	93 / 83	13	46	7.2	8.1
Kondziolka	2008	972	GKRS	All	48	14	97 / 87	11	42	8	7.4
Kondziolka	2009	125	GKRS	Convexity	31	14	86 / --	--	26	9.6	7.6
Bledsoe	2010	116	GKRS	All	70	15.1	99 / 92	--	--	23	17.5
Flannery	2010	168	GKRS	Petroclival	72	13	95 / --	26	49	14	7.7
Korah	2010	41	LINAC	All	60	14	94 / 94	--	--	2.4	4.5

Stereotactic Radiosurgery

First Author	Year	n	Technique	Location	Mean FU (months)	Mean/ Median Dose (Gy)	5yr/10yr PFS (%)	Clinical Improvement (%)	Tumor Regression (%)	Complication (%)	Mean/Median Tumor Vol (cc)
Skeie	2010	100	GKRS	Cav Sinus	82	12.4	94 / 91.6	21	22	6	7.4
Zada	2010	116	GKRS	All	75	16	99 / 84	--	26	8	3.4
Williams	2011	138	GKRS	Parasellar	84	13.7	95.4 / 69	--	78	10	7.5
Hayashi	2011	66	GKRS	Skull Base	46	12	99	--	82	1	6.6
dos Santos	2011	88	LINAC	Cav Sinus	87	14	92.5/82.5	51.1	73.8	19.3	--
Santacroce	2012	4565	GKRS	All	63	14	95.2/88.6	53.5	58	6.6	4.8
Unger	2012	173	LINAC	All	21	15[¶]	89.3/--	--	--	8.5[§]	4.7
Pollock	2012	251	GKRS	All	62.9	15.8	99.4/99.4	--	72.1	11.5	7.7
Starke	2012	255	GKRS	Skull Base	78	14	96/79	--	49	5.1	5.0

[¶] 15 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 external beam radiation therapy for patients largely with WHO grade I or presumed grade I meningiomas.

Fractionated External Beam Radiation Therapy											
				Progression-Free Survival							
First Author	Year	n	Technique	GTR	STR	STR+RT	RT Alone	Clinical Improvement	Tumor Shrinkage	Late Toxicity	Time Point
Adegbite	1983	114	EBRT	74%	34%	82%					10 yrs
Mirimanoff	1985	225	EBRT	80%	45%						10 yrs
Barbaro	1987	135	EBRT	96%	40%	68%				0%	crude
Taylor	1988	132	EBRT	77%	18%	82%					10 yrs
Glaholm	1990	117	EBRT	96%	43%	77%	46%	38%			10 yrs
Miralbell	1992	115	EBRT		48%	88%				16%	8 yrs
Mahmood	1994	254	EBRT	98%	62%						5 yrs
Goldsmith	1994	117	EBRT			77% 98%*				3.6%	10 yrs
Peele	1996	86	EBRT		52%	100%				5%	crude
Condra	1997	246	EBRT	80%	40%	87%				24%	10 yrs
Stafford	1998	581	EBRT	75%	39%						10 yrs
Nutting	1999	82	EBRT			83%				14%	10 yrs
Vendrely	1999	156	EBRT			79%		59%	29%	8%	
Pourel	2001	26	EBRT			76%				2.2%	8 yrs
Dufour	2001	31	EBRT			93%		71%	29%	3.2%	10 yrs
Jalali	2002	41	FSRT			100%		26.8%	22%	12.1%	3 yrs
Uy	2002	40	IMRT			93%			23%	5%	5 yrs
Pirzkall	2003	20	IMRT			100%		60%	25%	0%	3 yrs
Soyuer	2004	92	EBRT	77%	38%	91%				2.5%	10 yrs
Selch	2004	45	FSRT			97%		20%	18%	0%	3 yrs
Milker-Zabel	2005	317	IMRT			89%		42.9%	23%	0%	10 yrs
Henzel	2006	224	FSRT			97%		43.4%	46%	0%	3 yrs
Milker-Zabel	2007	94	IMRT			94%		39.8%	20%	4%	4.4 yrs
Hamm	2008	183	FSRT				93%		23.2%	2.7%	3 yrs
Litre	2009	100	FSRT			94%	94%	50–81%	9%	0%	5 yrs

Fractionated External Beam Radiation Therapy

First Author	Year	n	Technique	Progression-Free Survival GTR	STR	STR+RT	RT Alone	Clinical Improvement	Tumor Shrinkage	Late Toxicity	Time Point
Korah	2010	41	FSRT				94%			3%	5 yrs
Metellus	2010	53	FSRT			94%	94%	58.5%	30%	1.9%	10 yrs
Bria	2011	60	FSRT				95%	60%			1 yr.
Minniti	2011	52	FSRT				96% 93%	20%	23%	5.5%	3 yrs 5 yrs
Mahadevan	2011	16	FSRT				100%		19%	4%	2 yrs
Morimoto	2011	31	FSRT				87%		1%		5 yrs
Onodera	2011	27	FSRT				96.2%				5.3 yrs
Ohba	2011	281	FSRT/SRS	88.3%	63.7%	92.3%					5 yrs
Tanzler	2011	146	EBRT/FSRT/SRS			96% 93%	99% 99%			6.8%	5 yrs 10 yrs
Paulsen	2012	109	FSRT				98%	21%	5%		5 yrs

*Goldsmith et al, 10-year PFS 98% with treatment after 1980 when CT and MRI began to be used for treatment planning, versus 77% before 1980.

Table 6

Eight studies of stereotactic radiosurgery for atypical meningioma.

Stereotactic Radiosurgery for Atypical Meningioma						
Author (year)	**n**	**Follow-up[a]**	**Dose[a]**	**Local Control**	**Time Frame**	**Comments**
Stafford (2001)	13	47 mo	16 Gy	68 %	5yr actuarial	Majority were recurrent before SRS. 5y LC for Gr I 93%. 5y OS: 76% for Gr II vs 92% Gr I, worse CSS for Gr II. Predictors: Prior Surg or EBRT, larger tumor vol, location (non-basal)
Harris (2003)	18	46 mo	14.9 Gy	83%	5yr actuarial	Mean of 2 resections prior to SRS. 5y OS 59%. Better with smaller tumor vol and early SRS. Median neurologic progression: 15 mo early SRS vs 61 mo late SRS
Huffmann (2005)	15	35 mo	16 Gy	60 %	crude 18–36 mo	67% recurrent before SRS. 6 progressed after SRS, only 1 in field after 15 Gy, but all within the surgical bed. “Recurrence was essentially outside the SRS field”
Kano (2007)	12[b]	43 mo	18 Gy	48.3 %	2yr actuarial	All recurrent before SRS. 5y PFS 29.4% < 20 Gy vs 63.1% 20 Gy. 19 lesions progressed, 13 in field, and 6 out of field. Predictors: Gr III (vs II), dose < 20 Gy (vs 20 Gy)
Attia (2009)	24	26 mo	14 Gy	76% 52% 58%	1yr actuarial 2yr ” 5yr ”	Tumor vol and dose not predictive of LC, but CI was predictive. Mean CI 1.7 if recurrent vs 4.6 if no recurrence
Skeie (2010)	7	82 mo	12.4 Gy	0 %	mean 43 mo	100 cavernous sinus meningiomas, 7 Gr II. 5/7 progressed w/in 15 mo. Predictors: Gr II, tumor vol, dose, and suboptimal coverage[c]
Choi (2010)	25	28 mo	22 Gy[d]	90%[e] 90% [e] 62% [e]	1yr 2yr 3yr	15 treated immed after STR, 10 after progression. 9 failures: 3 local, 6 regional. Predictors: # recurrences, delayed SRS, age >60
Hardesty (2013)	32	52 mo	14 Gy	94%[f] 73% [f] 62% [f]	1yr 3yr 8yr	No significantly different from GTR or STR alone. No recurrence in 10 patients with GTR and SRS

n: number of patients, vol: volume, yr: year, mo: month, SRS: stereotactic radiosurgery, LC: local control, CSS: cause-specific survival, PFS: progression-free survival, Surg: surgery, EBRT: external beam radiation therapy, OS: overall survival, Gr: grade, vs: versus, w/in: within, Gy: Gray, CI: conformality index (treatment volume ÷ tumor volume), immed: imediately, LRC: locoregional control, STR: sub-total resection, #: number, signif: significant

[a]Mean or median.

[b]10 of the 12 had atypical primaries, 2 anaplastic.

[c] suboptimal coverage defined as <88%

[d] Choi *et al*, median marginal dose 22Gy in 1–4 fractions (median 1).

[e] Percentages refer to loco-regional control (i.e. SRS target & resection bed).

[f] Data derived from graph.

Table 7

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

Anaplastic (WHO Grade III) Meningioma							
Author (year)	**n**	**F/U[a] (study period)**	**Grading Scheme**	**Treatment Regimen**	**RT Dose[a]**	**Outcome**	**Comments**
Jaaskelainen (1986)	11	not reported (1953–1980)	Modified WHO 1979	Post-op & salvage surgery alone or surgery + EBRT	not reported	**PFS** 5 yr 22%	Atypia and anaplasia developed in previously benign tumors without radiotherapy. 4 of 5 anaplastic tumors treated w/ surg + EBRT recurred. EBRT doses not reported.
Milsoevic (1996)	42	Not reported (1966–1990)	Modified WHO 1979	Post-op & salvage surg + EBRT or salvage EBRT alone.	**EBRT** 50 Gy	**CSS** 2 yr 63% 5 yr 34%	Malignancy often diagnosed (60%) by brain invasion (60%), some hemangiopericytomas. Negative predictive fxs (CSS): age ≥58, EBRT before 1975, dose <50Gy. Morbidity 3.4%. Recommend immediate post-op EBRT.
Dziuk (1998)	38	29–39 mo[b] (1984–1992)	Russell & Rubinstein 1977 [R&R 1977]	Initial & salvage surg alone or with EBRT	**EBRT** 54Gy	**PFS** 2 yr 24% 5 yr 25%	5yr PFS: 39% after GTR, 0% STR. 28% GTR alone, 57% GTR+EBRT. Intital post-op EBRT improved 5yr PFS 15% to 80%, and salvage EBRT 2yr PFS 50% to 89%, but no benefit at 60 mo. 11 had hemangiopericytoma. No distant failures.
Hug (2000)	16	59 mo (1973–1995)	WHO 1993	Post-op & salvage photon + proton EBRT	**EBRT** photon + proton 58 CGE	**LC** 5 yr 52% 8 ys 17%	LC & OS improved w/ EBRT ≥60 Gy. 5 & 8yr LC 100% & 33% w/ ≥60 CGE versus 0% w/ <60 CGE. Late morbidity 9%.
Mattozo (2007)	5	42 mo (1992–2004)	WHO 2000	Post-op & salvage SRS or stereotactic EBRT	**SRS** 15.5 Gy **EBRT** 49.3Gy	**PFS** 3 yr 0%	All patients had recurrent tumors. Median SRS treatment vol 2.2cc, median EBRT vol 21.3cc. 77% of recurrences were within the original resection cavity.
Kondziolka (2008)	29	48 mo (not reported)	Based upon “previous histo-path”	Post-op & salvage single fraction SRS	**SRS** 14 Gy	**LC** 15mo 17% 5yr 9%[¶]	Median tumor vol 7.4cc. 5y CSS 22%[¶] Morbidity 7%, including symptomatic edema in 4%
Boskos (2009)	5	32 mo (1999–2006)	WHO 1993	Post-op & salvage photon + proton EBRT. 1 patient hypofractionated protons alone	**EBRT** photon + proton 65 CGE	**Mean RFI** 23 mo	Median CTV 151cc. Mean RFI for grade II tumors 28.3mo. OS & CSS improved w/ EBRT >60 Gy, and possibly further w/ >65 Gy. Late morbidity in 1 patient, necrosis.
Rosenberg (2009)	13	not reported (1984–2006)	WHO 2007	Post-op & salvage EBRT or SRS. 2 received systemic therapy (1 temozolomide, 1 immunotherapy)	**EBRT** 50–60 Gy **SRS** 14–24 Gy 5 Gy x 5	**PFS** 1 yr 52% 2 yr 17% 3 yr 8.7%	Median time to recurrence 9.6 mo. Med OS 2.5 yr w/o vs 5.4 yr w/ initial EBRT (p=.13). 5 & 8 yr OS 47.2%, 12.2%. RT morbidity 2 patients, both necrosis. Recommend upfront RT.
Sughrue (2010)	63	60 mo (not reported)	WHO 2007	Post-op fractionated EBRT & some salvage brachy or SRS, newly diagnosed & recurrent. 25% pre-operative embolization	**EBRT** doses not reported	**PFS** 2yr 80% 5yr 57% 10yr 40%	Mean tumor vol 78cc. 2,5&10 yr OS 82%, 61%, 40%. Better survival with NTR than with GTR. Signif neuro morbidity from attempted GTR.

Anaplastic (WHO Grade III) Meningioma							
Author (year)	**n**	**F/U[a] (study period)**	**Grading Scheme**	**Treatment Regimen**	**RT Dose[a]**	**Outcome**	**Comments**
El-Khatib (2011)	7	60 mo (1990–2003)	WHO 2007	Post-op & salvage single fraction SRS, newly diagnosed & recurrent	**SRS** 14 Gy	**PFS** 3yr 57% 5yr 57% 10yr 43%	Median tumor vol 4.8cc. PFS 57% 5yr, 43% 10yr. Negative predictive fx (tumor control) age ≥50. Morbidity 3.5%.
Pollock (2012)	13	38 mo (1990–2008)	WHO 2000 & 2007	Post-op & salvage single fraction SRS, newly diagnosed & recurrent	**SRS** 15 Gy	**CSS** 1 yr 69% 5 yr 27%	Median tumor vol 14.6cc. Negative predictive fxs (CSS): prior EBRT & tumor vol >14.6cc. Morbidity 26%. Emphasize early SRS.

n: number of patients, F/U: follow-up, RT: radiation therapy, WHO: World Health Organization, Post-op: post-operative, EBRT: external beam radiation therapy, PFS: progression-free survival, w/: with, surg: surgery, fx(s): factor(s), CSS: cause-specific survival, mo: month, GTR: gross total resection, STR: subtotal resection, yr: year,LC: local control, CGE: cobalt Gray equivalent), vol: volume, histo-path: histo-pathology, RFI: relapse-free interval, CTV: clinical target volume, OS: overall survival,SRS: stereotactic radiosurgery, brachy: brachytherapy, NTR: near total resection (>90% removal), neuro: neurological, vs: versus.

[¶]Actuarial percentage measured from graph.

[a]Mean or median

[b]follow-up listed by study groups, and varied accordingly.