Cyberknife Stereotactic Radiosurgery for Treatment of Atypical (Who Grade II) Cranial Meningiomas

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BACKGROUND: The optimal management of subtotally resected atypical meningiomas is unknown.

OBJECTIVE: To perform a retrospective review of patients with residual or recurrent atypical meningiomas treated with stereotactic radiosurgery (SRS).

METHODS: Twenty-five patients were treated, either immediately after surgery (n = 15) or at the time of radiographic progression or treatment failure (n = 10). SRS was delivered to with a median marginal dose of 22 Gy (range, 16-30) in 1 to 4 fractions (median, 1), targeting a median tumor volume of 5.3 cm^3 (range, 0.3-26.0).

RESULTS: With a median follow-up time of 28 months (range, 3-67), the 12-, 24-, and 36-month actuarial local and regional control rates for all patients were 94%, 94%, 74%, and 90%, 90%, 62%, respectively. There were 2 cases of radiation toxicity. On univariate analysis, the number of recurrences before SRS ($P = .046$), late SRS (ie, waiting until tumor progression to initiate treatment) ($P = .03$), and age at treatment ≥60 years ($P = .01$) were significant predictors of recurrence. Of the 20 radiation-naïve patients, 2 patients failed with the targeted lesion and 3 elsewhere in the resection bed, resulting in 12-, 24- and 36-month actuarial local and regional control rates of 100%, 100%, 73% and 93%, 93%, 75%, respectively. The overall locoregional control rates at 12, 24, and 36 months were 93%, 93%, and 54%, respectively.

CONCLUSION: Irradiation of the entire postoperative tumor bed may not be necessary for the majority of patients with subtotally resected atypical meningiomas. Patients in this series achieved outcomes comparable to that of historical control rates for larger volume, conventionally fractionated radiotherapy.

KEY WORDS: Atypical meningioma, CyberKnife, Radiation, Stereotactic radiosurgery, WHO Grade II meningioma

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Intracranial meningiomas are the second most frequent primary brain tumor, representing 20% of all intracranial tumors.[1,2] The World Health Organization (WHO) histological grading scheme is the most commonly used classification, with benign, atypical, and malignant (anaplastic) meningiomas classified as WHO grade I, II, and III, respectively.[3] Ninety percent of meningiomas are benign, and WHO grade II and III tumors occur approximately 10% and <2%, respectively.

Compared with WHO grade I, WHO grade II meningiomas carry a significantly worse prognosis, with increased recurrence and mortality rates.[4-9] Surgery is the primary treatment, and the extent of surgical resection is crucial. Goyal et al,[10] in their series of 22 patients, reported 10-year local control rates of 87% and 17% after gross total resection (GTR) and subtotal resection (STR) of atypical meningiomas, respectively. Although the role of postoperative radiotherapy has been studied most extensively in the setting of benign

ABBREVIATIONS: **EBRT**, external beam radiotherapy; **GTR**, gross total resection; **GTV**, gross tumor volume; **SRS**, stereotactic radiosurgery; **SRT**, stereotactic radiotherapy; **STR**, subtotal resection; **WHO**, World Health Organization

meningiomas,[5,11] many advocate adjuvant radiation for patients with subtotally resected atypical meningiomas because of their high rate of recurrence.[12-14] Traditionally, the entire tumor bed of a resected atypical meningioma with margin has been irradiated (eg the entire preoperative tumor volume plus a 1- to 3-cm margin,[5,13] enhancing tumor plus a 3- to 4-cm margin,[6] and operative bed plus 1 cm margin[15]), often resulting in a large volume of normal brain receiving radiation. Whether these large volumes are necessary is unclear.

Because of its rarity and the recent adaptation of its histological classification, there are limited data on the best adjuvant radiotherapy course for atypical meningiomas. We retrospectively reviewed the outcomes of patients with subtotally resected and recurrent WHO grade II meningiomas treated with stereotactic radiosurgery (SRS) at our institution. Herein, we present our results suggesting that irradiation of the entire tumor bed can be avoided in favor of radiosurgery to treat the residual tumor in well selected patients with subtotally resected atypical meningiomas.

METHODS AND MATERIALS

Patients

Patient data were obtained from an institutional review board-approved, prospectively maintained database of patients treated by use of the CyberKnife Robotic Radiosurgical System (Accuray, Sunnyvale, California) at the Stanford University Medical Center. All patients underwent a prior resection and had a histologically confirmed diagnosis of WHO grade II meningioma.[3] Of the 29 patients treated from February 2000 to March 2008, follow-up information was lacking in 4 patients, yielding 25 patients evaluable clinically and radiographically. Five of 25 patients had received prior radiotherapy, yielding 20 radiation-naïve patients.

Patient characteristics are listed in Table 1. Twelve women and 13 men underwent SRS at a median age of 57 years (range, 23-80 years). Ninety-two percent had a Karnofsky performance score of ≥80%. The median number of prior treatments (surgery and/or radiotherapy) was one (range, 1-9). Patients were referred for SRS treatment at the following times: (1) immediately after surgery because of an area of residual disease seen on postoperative imaging (n = 15 [60%]); (2) at the time of radiographic progression of residual tumor after an initial period of observation following STR (ie, progression of existing tumor) (n = 3 [12%]); (3) for recurrent tumor after surgery and radiation (n = 5 [20%]); or (4) for recurrent tumor after GTR (ie, new tumor formation) (n = 2 [8%]). The initial choice to treat or observe was based on the medical decision making between the patient and the referring physician.

Five patients had prior radiotherapy, including one patient who had both conventionally fractionated external beam radiotherapy (EBRT) (56 Gy) and LINAC-based SRS (18 Gy), 18 and 11 years before receiving CyberKnife SRS. The second patient had received EBRT (54 Gy) 6 months before SRS. Three patients had been treated with SRS alone (ie, no prior EBRT) 7, 39, and 50 months earlier. Patients with prior SRS were referred for additional treatment owing to (1) development of a new tumor within the resection cavity (n = 1), (2) failure at the previously treated target (n = 2), and (3) marginal failure at the posterior border of the previous SRS target (n = 1).

TABLE 1. Patient and Treatment Characteristics: All Patients[a,b]

Patient Characteristics	
Age at treatment, y	
Median	57 (range, 23-80)
Sex	
Female	12 (48%)
Male	13 (52%)
Karnofsky performance status	
Median	90% (range, 60-90%)
60%	1 (4%)
70%	1 (4%)
80%	4 (16%)
90%	19 (76%)
Number of prior treatments	
Median	1 (range, 1-9)
Number of previous surgeries	
Median	1 (range, 1-6)
1	19 (76%)
2	5 (20%)
6	1 (4%)
Timing of SRS	
Early to treat residual tumor seen on postoperative imaging	15 (60%)
Late (at the time of radiographic progression)	10 (40%)
Prior radiation	
External beam radiation (54-56 Gy)	2* (8%)
Gamma knife (12-15 Gy)	2
LINAC (18 Gy)	2*
Treatment Characteristics	
Number of lesions treated	
Median	1 (range, 1-5)
Total number of lesions treated	34
Sessions	
1	18 (53%)
2	2 (6%)
3	13 (38%)
4	1 (3%)
Target volume (cm^3)	
Median	5.3 (range, 0.3-26.0)
Marginal prescription dose (Gy)	
Median	21 (range, 16-30)
Maximum dose (Gy)	
Median	27 (range, 20-39)
Prescription isodose line (%)	
Median	80 (range, 62-91)
Biologically effective dose single session equivalent ($\alpha/\beta = 4$) (Gy_4)	
Median	18 (range, 12-21)

[a] SRS, stereotactic radiosurgery.
[b] One patient had received external beam radiation and LINAC SRS before presenting for CyberKnife SRS.

Early SRS was defined as radiosurgery administered shortly after surgery to treat residual tumor seen on postoperative imaging. Late SRS was defined as treatment initiated after evidence of radiographic tumor progression.

Radiosurgery Dose and Fractionation

The prescribed dose and fractionation schedule were based on the preference of the treating physicians, size of the lesion, proximity of the lesion to nearby critical structures, and dose of prior radiation. Treatment characteristics are listed in Table 1. SRS was delivered to a median marginal dose of 21 Gy (range, 16-30 Gy) prescribed to the median 80% isodose line (range, 62-91%), targeting a median tumor volume of 5.3 cm^3 (range, 0.3-26.0 cm^3). The median maximum dose within the target was 27 Gy (range, 20-39 Gy). SRS was delivered in 1 to 4 fractions (median, 1).

Because of the range in the prescription doses and the fraction schemes used in this series, the biologically effective dose and equivalent single-session dose were derived from the linear quadratic model.[16] Although the α/β ratio for WHO grade II meningiomas is not known, the lower and upper limits of α/β ratio estimates of WHO grade I meningioma have been calculated to be 2.7 to 3.9.[17] Therefore, we selected a conservative α/β ratio estimate of 4 to calculate equivalent single-session doses for WHO grade II lesions. Conversion of the various fractionation schemes used in this series with the linear quadratic formula yielded a median single-session equivalent dose (α/β = 4) of 18 Gy_4 (range, 12-21 Gy_4).

Radiosurgical Technique

The CyberKnife Robotic Radiosurgical System (Accuray, Sunnyvale, California) was used to deliver the radiosurgical treatments. A high-resolution thin-slice (1.25 mm) computed tomogram was obtained using a GE Light Speed 8i or 16i Scanner (Milwaukee, Wisconsin) after administration of 125 mL of Omnipaque intravenous contrast (iohexol, 350 mg I/mL; Nycomed, Inc., GE Healthcare, Princeton, New Jersey). Stereotactic magnetic resonance imaging (MRI) scan was obtained and fused to the stereotactic CT scan to improve target identification.

The neurosurgeon, radiation oncologist, and radiation physicist performed tumor delineation, dose selection, and planning. The gross tumor volume (GTV) was defined as the residual or recurrent enhanced tumor seen on imaging. The radiosurgical dose was prescribed to cover the GTV, with no additional margin. Treatment plans were generated in an iterative manner using the CyberKnife nonisocentric inverse treatment planning software. An example of a treatment plan is shown in Figure 1.

Quality of treatment plans was assessed by evaluating target coverage, dose heterogeneity, and conformity. Digitally reconstructed radiograms were computationally synthesized to allow near real-time patient tracking throughout radiosurgery. Informed consent for treatment was obtained for all patients. Patients received 4 mg of dexamethasone immediately after each treatment. For multisession treatments, the typical inter-fraction time interval was 24 hours.

Follow-up

MRI was repeated at 3-month intervals during the first year following SRS and every 4 to 6 months thereafter. Brain MRI results were used to score local and regional failures. Local failure was defined as progression of the treated lesion (ie, enlargement of existing tumor). Regional failure was defined as a recurrence elsewhere within the resected tumor bed (ie, new tumor within the resection cavity).

Toxicity

Patients were monitored for possible radiation induced adverse events with both clinical follow-up and imaging studies. Toxicity is defined as any unfavorable and unintended change in the sign or symptom considered possibly, probably, or definitely related to SRS. The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (http://ctep.cancer.gov) was used for grading of adverse events.

Statistical Analysis

Overall survival, local, regional, and locoregional control rates were calculated using the Kaplan-Meier product-limit method[18] using Stat View, version 5.0.1 (SAS Institute Inc., Cary, North Carolina). The effects of prognostic variables were assessed using the Cox proportional hazards analysis.[19] All factors with a P value of $\leq .2$ on univariate analysis were entered into the model. Time of local, regional, and locoregional control rates were calculated from the date of radiosurgery to the last MRI scan that showed recurrence or tumor control. The overall survival rates were calculated from both the date of initial diagnosis and the date of SRS.

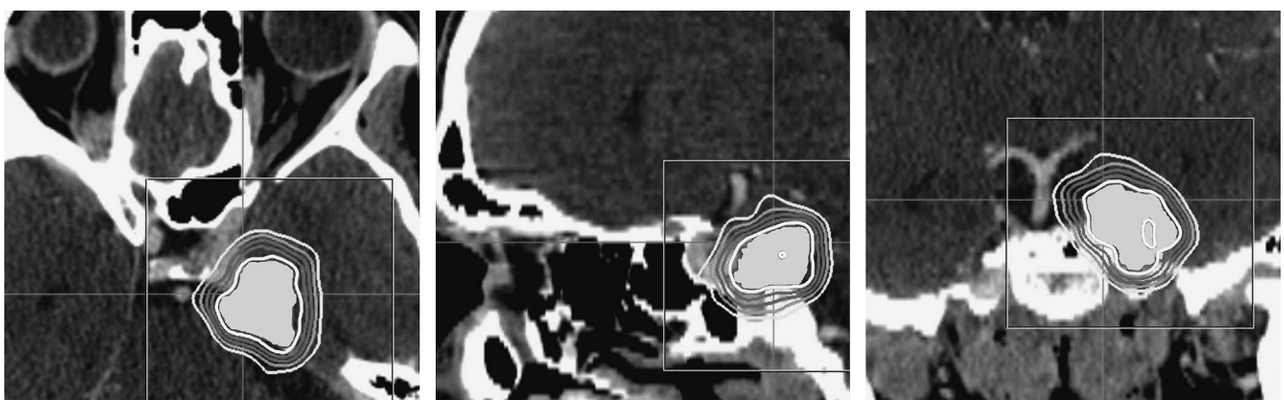

FIGURE 1. *An example of a treatment plan. Thirty Gy in 3 fractions was prescribed to the 80% isodose line to treat a 5.48-cm^3 target. The GTV is shown in shaded gray. Going from the innermost to outermost lines are 80% (white), 70%, 60%, 50%, and 40% isodose lines. GTV, gross tumor volume.*

RESULTS

Local and Regional Control

Overall, recurrences were seen in 9 (36%) of 25 patients. Tumor recurred in 3 patients within the targeted region (local failures), in 5 patients with a new tumor elsewhere in the tumor resection bed (regional failures), and in 1 patient both within and outside the radiosurgery target (ie, both local and regional failures). With a median follow-up time of 28 months (range, 3-67 months), the 12-, 24-, and 36-month actuarial local control rates for all patients were 94%, 94%, and 74%, respectively; the 12-, 24-, and 36-month actuarial regional control rates were 90%, 90% and 62%, respectively. The overall, combined locoregional control rates at 12, 24, and 36 months were 90%, 90%, and 47%, respectively (Figure 2). On univariate analysis, the number of recurrences (as a continuous variable) before presenting for CyberKnife SRS (P = .046), early SRS (ie, immediate [within 6 months] postoperative SRS to treat the residual tumor) (P = .03), and age at treatment (as a continuous variable) (P = .04) were predictive of locoregional control. Age ≥60 years (as a nominal variable) was a significant predictor of locoregional failure (P = .01). Sex, target volume, number of SRS fractions, and biologically effective dose were not significant predictors of recurrence.

Radiation-Naïve Patients

Owing to normal tissue tolerance, prior history of radiotherapy limits the field size and/or prescription dose for subsequent treatments. To eliminate this potentially confounding factor, additional analyses were performed on the 20 patients who presented without prior radiotherapy. Five of the 20 patients were treated because of radiographic evidence of tumor recurrence after an initial period of observation, with a median time from the last surgery to SRS of 22 months (range, 13-46 months). Three of these 5 patients had known residual tumor on postoperative imaging but were observed until tumor progression (ie, enlargement of existing tumor); the other 2 patients had initially been treated with GTR and referred for SRS at the time of tumor recurrence (ie, new tumor formation). The remaining 15 patients were offered upfront SRS owing to the presence of residual tumor on postoperative imaging (median time to SRS of 1 month; range, 1-7 months). The patient characteristics of the radiation-naïve group are listed in Table 2. Recurrence was observed in 5 patients: 2 local and 3 regional failures. With a median follow-up period of 22 months (range, 3-67 months), the actuarial local control rates at 12, 24, and 36 months were 100%, 100%, and 73%, respectively; regional control rates were 93%, 93%, and 75%, respectively. The overall control rates (ie, locoregional) at 12, 24, and 36 months were 93%, 93%, and 54%, respectively (Figure 3).

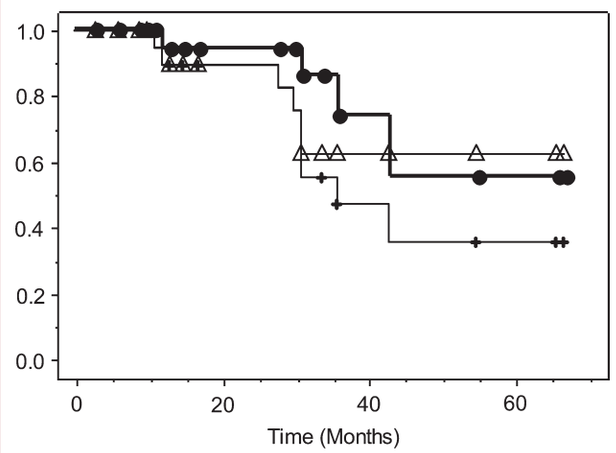

FIGURE 2. *Kaplan-Meier local control ([●]), regional control ([△]), and overall locoregional control ([+]) rates for all patients, calculated from the date of SRS. The 12-, 24-, and 36-month actuarial local control rates ([●]) were 94%, 94%, and 74%, respectively; the 12-, 24-, and 36-month actuarial regional control rates ([△]) were 90%, 90% and 62%, respectively. The overall locoregional control rates ([+]) at 12, 24, and 36 months were 90%, 90%, and 47%, respectively. SRS, stereotactic radiosurgery.*

Recurrences in Radiation-Naïve Patients

Characteristics of the 5 radiation-naïve patients who had recurrences are listed in Table 3. The median time to recurrence from the date of SRS was 15 months (range, 11-29 months). Two patients had local failures (ie, enlargement of the primary lesions treated with radiosurgery) and received additional treatments: Patient 1 was managed with surgery followed by 60 Gy EBRT using intensity-modulated radiation therapy to treat the tumor bed. Patient 2 underwent a surgical resection, followed by postoperative fractionated CyberKnife SRS to treat a small area of residual tumor (30 Gy in 3 fractions prescribed to the 80% isodose line, targeting a 0.49-cm^3 volume); this patient remains recurrence free at the time of last follow-up, 9 months following the second course of SRS.

TABLE 2. Characteristics of the 20 Radiation-Naïve Patients

Patient Characteristics	
Age at treatment, y	
Median	57 (range, 23-80)
Sex	
Female	9 (45%)
Male	11 (55%)
Karnofsky performance status	
80%	4 (20%)
90%	16 (80%)
Number of prior surgeries	
1	16 (80%)
2	4 (20%)
Indications for treatment	
Subtotally resected tumor (early treatment)	15 (75%)
Local recurrence after observation (late treatment)	5 (25%)

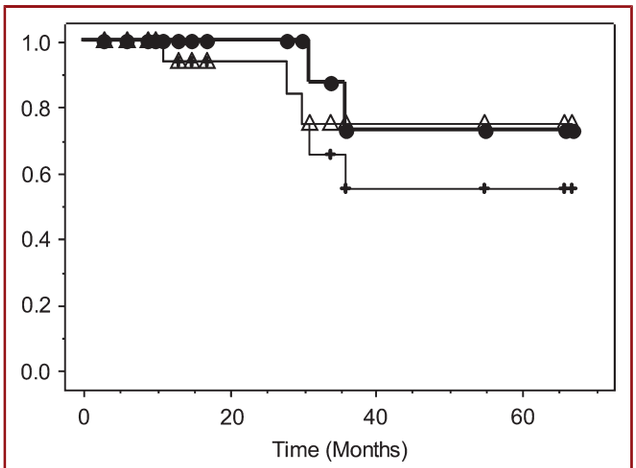

FIGURE 3. *Kaplan-Meier local control ([●]), regional control ([△]), and overall locoregional control ([+]) rates for radiation-naïve patients, calculated from the date of SRS. The 12-, 24-, and 36-month actuarial local control rates ([●]) were 100%, 100%, and 73%, respectively; the 12-, 24-, and 36-month actuarial regional control rates ([△]) were 93%, 93% and 75%, respectively. The overall locoregional control rates ([+]) at 12, 24, and 36 months were 93%, 93%, and 54%, respectively. SRS, stereotactic radiosurgery.*

Three patients had regional failures (ie, recurrence of new tumors elsewhere in the resection bed, distant from the radiosurgery target volumes). Patient 3 underwent CyberKnife SRS alone to treat the recurrent tumor (18 Gy in a single session prescribed to the 76% isodose line targeting a 0.5-cm^3 volume); this patient remains free of disease 12 months following the second course of SRS. Patient 4 was managed with surgery followed by postoperative CyberKnife SRS to treat an area of residual tumor; this patient developed another regional recurrence 6 months later and was referred for EBRT. A recurrent tumor located anterior to the prior radiosurgical field was diagnosed in patient 5 on follow-up MRI scan. The patient's recurrent tumor is scheduled to be treated with SRS.

Survival

Overall, 3 of 25 patients have died at the time of this analysis. Calculated from the time of initial diagnosis, with a median follow-up time of 4 years (range, 1.1-21.6 years), the actuarial overall survival rates at 3 and 5 years are 96% and 91%, respectively. Calculated from the time of CyberKnife radiosurgery, the actuarial overall 3-year survival rate is 90% (median follow-up time of 3 years; range, 0.7-9.0 years).

Toxicity

There were 2 cases of radiation-induced adverse events. The first is a case of a grade 1 CNS necrosis in which a follow-up MRI scan showed evidence of radiation necrosis within the bilateral frontal lobe 5 years following SRS. Because the patient was neurologically asymptomatic, no intervention was initiated. The patient continues to be followed closely and is without evidence of tumor progression.

The second is a case of a grade 3 hydrocephalus. Six months following SRS, a patient developed hydrocephalus from obstruction

TABLE 3. Recurrences in Radiation-Naïve Patients[a]

Patient No.	Area	Interval from surgery to SRS (mo)	Indication for SRS	SRS dose (Gy)	No. sessions	Rx isodose line (%)	Target volume (cm^3)	Interval from SRS to recurrence (mo)	Treatment of recurrence
Local failure									
1	Right fontal	11	Multifocal recurrence after observation	24	3	62	#1: 3.1	15	Surgery and EBRT
							#2: 0.7		
							#3: 0.3		
2	Inferior falx	2	Residual after surgery	20	1	81	2.8	29	Surgery and postoperative multisession SRS
Regional failure									
3	Left parasagittal	20	Recurrence after observation	22.5	3	69	8.4	4	CyberKnife SRS
4	Right frontoparietal	1	Residual after surgery	18	1	81	9.7	12	Surgery and postoperative CyberKnife SRS followed by surgery and EBRT for 3rd recurrence
5	Frontoparietal parasagittal	7	Residual after surgery	24	3	75	9.4	11	Scheduled for CyberKnife SRS

[a]SRS, stereotactic radiosurgery; EBRT, external beam radiotherapy.

TABLE 4. Selected Literature Review of Atypical Meningiomas Treated With Conventionally Fractionated External Beam Radiotherapy[a]

Authors	Histology	Total, n	Atypical, n	Surgery	Dose, Gy (range)	RT Target Volume	Outcomes for Atypical Meningioma Patients	F/U Median, mo
Goldsmith et al, 1994[5]	Benign and malignant	140	23 malignant[b]	STR	54 (45-69)	Preoperative tumor volume + 1- to 3-cm margin	48% 5-y PFS 58% 5-y OS	40
Milosevic et al, 1996[6]	Atypical and Malignant	59	17[b]	15 GTR, 35 STR, 7 biopsy only or unknown	50 (40-60)	Enhancing tumor + 3- to 4-cm margin	34% freedom from progression 28% 5-y OS 34% 5-y CSS	40
Hug et al, 2000[15]	I and II	31	15	8 GTR, 21 STR, 2 biopsy	50-68	CTV = gross disease, operative bed, hyperostotic bone, and areas of dural thickening + 1-cm margin	38% 5-y LC 89% 5-y OS	59
Coke et al, 1998[13]	Atypical and malignant	17	9	12 GTR, 4 STR, 1 unknown	61 (mean)	Preoperative tumor volume + 2- to 2.5-cm margin	87% 5-y OS	87
Pasquier et al, 2008[7]	II and III	119	82	71% GTR	55 (mean) (40-66)	Not reported	68% 5-y OS 62% 5-y DFS	49

[a]CSS, cause specific survival; CTV, clinical tumor volume; DFS, disease-free survival; F/U, follow-up (median); GTR, gross total resection; OS, overall survival; PFS, progression free survival; LC, local control; RFS, relapse-free survival; RT, radiotherapy; STR, subtotal resection.
[b] Based on older classification (ie, pre-2000).

of the fourth ventricle, thought to be due to radiation-induced edema. The patient was treated with an endoscopic third ventriculostomy and remains well without evidence of tumor progression.

DISCUSSION

Atypical (WHO grade II) meningiomas are uncommon and carry a worse prognosis than benign (WHO grade I) lesions. Compared with the 5-year progression-free survival rate of 89% for benign meningiomas, the 5-year progression-free survival rate was 48% for subtotally resected "malignant" meningiomas treated with postoperative external beam radiation.[5] Because this study by Goldsmith et al predates the WHO revised grading system, it is not possible to distinguish the outcomes between WHO grade II and III patients. Milosevic et al,[6] also using an older classification system, reviewed 59 patients with atypical (n = 17) or malignant (n = 42) meningiomas treated with postoperative external beam radiation and reported disease progression in 39 patients (66%). Hug et al[15] analyzed 15 patients with atypical meningiomas treated with postoperative radiotherapy; the 5-year actuarial local control rate in their series was 38%.

Surgery is the primary treatment of atypical meningiomas. The extent of surgical resection is important as the reported 10-year-local control rates are 87% and 17% after GTR and STR, respectively.[10] Given the high risk of recurrence, adjuvant radiotherapy is advocated for subtotally resected WHO grade II lesions. However, owing to the rarity of atypical meningiomas and the relatively recent adaptation of the histopathologic classification scheme, data are lacking as to the best adjuvant radiation technique, including target definition, dose, and fractionation. Traditionally, large treatment volumes, such as the entire preoperative tumor volume plus a 1- to 3-cm margin,[5,13] enhancing tumor plus a 3- to 4-cm margin,[6] and operative bed plus 1-cm margin,[15] have been used with conventionally fractionated EBRT to a dose of 50 to 61 Gy. An important issue in irradiating a large brain volume is the risk of late complications, including neurocognitive dysfunction.[20] This issue is especially pertinent in this group of patients with a prolonged life expectancy. In our series, the 5-year overall survival rate, calculated from the time of diagnosis, is 91%. Similarly, high 5-year overall survival rates of 68 to 89% are reported in modern radiotherapy series (Table 4). Therefore, late sequelae of radiotherapy are a serious concern, and methods to decrease the amount of normal brain being irradiated would appear desirable. Moreover, conventionally fractionated radiotherapy to doses of 50 to 60 Gy causes permanent destruction of the hair follicles, resulting in permanent alopecia. The follicle dose at which 50% of the patients develop permanent alopecia has been calculated to be 43 Gy.[21] The effect of alopecia on patients' quality of life has been

TABLE 5. Selected Literature Review of Atypical Meningiomas Treated With Stereotactic Radiosurgery or Stereotactic Radiotherapy[a]

Authors	Histology	Total, n	Atypical, n	Additional RT	Median Marginal Dose (Gy) (range)	Outcomes for Atypical Meningioma Patients	F/U Median, mo
Hakim et al, 1998[25]	I, II, and III	127	26	Yes (number not reported)	15	83% 4-y OS; Median time for freedom from progression: 24 mo	31
Stafford et al, 2001[26]	I, II, and III	190	13	32 patients of 190 in the series	16	76% 5-y cause-specific survival 68% 5-y LC	40
Harris et al, 2003[27]	II and III	30	18	Yes[b]	15 (mean)	83% 5-y PFS 59% 5-y OS	28
Milker-Zabel et al, 2005[4][c]	I and II	317	26	No	57.6 in 1.8 1 Gy fractions to tumor + 2- to 3-mm margin	89% 5-y RFS	68
Huffmann et al, 2005[28]	II	15	15	n = 1 EBRT before SRS	16 (14-18)	n = 6 failures between 18 and 36 mo	35
Mattozo et al, 2007[29]	II and III	25	11	3 of 25 patients treated with EBRT	SRS: 16 (12-18) SRT: 49 (25-54)	83% 3-y PFS 2/19 SRS failure; 2/5 SRT failure	42
Kano, 2007[30]	II and III	12	10	n = 2 EBRT	19 (12-20)	81% 5-y OS; 48% 2-y PFS	43 (mean)
Current series	II	25	25 (20 radiation naïve patients)	n = 5	22 (16-30) in 1-4 fractions	73%, 75%, and 54% 3-y local, regional, and overall control rates for radiation-naïve patients; 91% 5-y OS	28

[a]RT, radiotherapy; F/U, follow-up (median); EBRT, external beam radiotherapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; OS, overall survival; PFS, progression free survival; LC, local control; STR, subtotal resection.
[b]Of the 30 total patients in the series (12 patients with malignant and 18 with atypical meningioma), 10 patients received more than one SRS, and 24 patients received adjuvant fractionated EBRT to a mean dose of 54 (± 4) Gy. The authors do not report how many of the atypical group received additional radiotherapy.
[c]Used SRT. Thirty-eight patients underwent STR, 41 had biopsies only, and 97 patients had no surgery.

better studied in the setting of chemotherapy. Multiple studies have shown alopecia to be one of the most important side effects of cancer treatment, with associated lower scores on quality-of-life measurements, lower self-esteem, poorer body image, decrease in sensuality and sexuality, and reluctance to continue working.[22]

To this end, SRS is an attractive option. First, the steep dose-gradient away from the target minimizes irradiation of the surrounding normal brain. Second, permanent alopecia is not likely to occur with radiosurgery.[23] Third, the short treatment duration (1-5 days compared with 6 weeks for conventionally fractionated radiation) makes it more convenient for patients and their families, in particular, those living distant from a radiation facility. However, the biggest potential detriment to a patient's health and quality of life is tumor recurrence. Therefore, the use of SRS could not be justified unless the treatment outcomes from SRS are at least comparable to larger field, conventionally fractionated radiotherapy. A selected review of the literature for atypical meningiomas treated with fractionated radiotherapy is shown in Table 4. The 3-year local and locoregional control rates of 73 and 54% for radiation-naïve patients reported herein compares favorably to the historical outcomes (reported control rates of 34%-68%[5-7,13,15]) using fractionated EBRT targeting the tumor bed (Table 4).

The safety and efficacy of SRS has been well established in the treatment of benign meningiomas.[24-26] Because of its relative rarity, there are fewer published data on the role of SRS in the treatment of WHO grade II meningiomas. A review of SRS literature on treatment of atypical meningiomas is summarized in Table 5. Because most series report on a heterogeneous group of patients, often combining WHO grade I, II, and/or III lesions and patients with and without prior radiation, it is difficult to evaluate the treatment outcomes of the patients with WHO grade II meningioma separately. The 4- to 5-year overall survival rates of 59 to 91% among patients with atypical meningioma historically achieved with SRS (Table 5) are comparable to the overall survival rates of external beam radiation patients (Table 4), suggesting no overall survival benefit to large field radiation.

Harris and colleagues[27] treated 30 patients (18 atypical and 12 malignant meningiomas) with gamma knife radiosurgery, in combination with surgery and fractionated EBRT. With a median follow-up period of 2.3 years (range, 0.1-11.4 years), the 5-year progression-free survival rate for atypical lesions was 83%; in addition, there was a trend toward improved progression-free survival for patients treated with early SRS (ie, soon after craniotomy rather than waiting until tumor progression). Stafford et al performed gamma knife SRS on 190 patients with meningiomas. Included in the series were 13 atypical and 9 malignant tumors, a majority of which were treated in conjunction with EBRT. The 5-year local control rate for atypical meningiomas was 68%. History of external beam radiation, tumor location, and tumor volume were significant predictors of local failure; however, because benign meningiomas were included in this analysis, it is not possible to ascertain if such factors would be predictive in the setting of atypical meningioma.[26] Huffmann and colleagues[28] treated 21 atypical meningiomas in 15 patients with gamma knife SRS. Four patients had residual tumor, ten had recurrent tumors after 1 to 4 surgeries (median, 2), and one had prior EBRT. The authors report 6 failures, occurring 18 to 36 months following radiation. Recurrences were in the region of the surgical approach or resection bed in 4 patients (27%) and marginal recurrence in 2 (13%). Hakim and coworkers[25] published the results of 155 meningiomas in 127 patients, including 26 atypical meningiomas. Sixty-nine percent had one or more prior treatment, including radiation. For the patients with atypical meningiomas, the median time for freedom from progression was 24.4 months, with a 3-year survival probability of 83%. Mattozo et al reviewed the results of LINAC-based SRS (median marginal dose of 15.5 Gy; range, 12-18 Gy) and stereotactic radiotherapy (SRT) (median dose 49.3 Gy; range, 25-54 Gy) to treat 52 recurrent meningiomas in 25 patients. Included in this were 24 WHO grade II meningiomas in 11 patients; the 3-year progression-free survival rate was 83% (100% and 33% for SRS and SRT treatments, respectively).

In our series of 25 patients with atypical meningioma treated with CyberKnife SRS, 3 factors were predictive of increased risk of locoregional failure. First, the more recurrences a patient had before presenting for CyberKnife SRS, the greater the likelihood of progression after radiosurgery (P = .046). Patients with multiple prior treatment failures were referred to us for SRS because they had few other treatment options remaining. Both tumor biology and tumor hypoxia may contribute to the increased risk of treatment failure. The biology of tumors that are multiply recurrent despite repeated therapies is probably more aggressive and difficult to treat. In addition, prior surgical and radiation effects on the brain's vasculature will create a more hypoxic environment, leading to relative radiation resistance. Second, the tumors that were treated early (ie, within 6 months of craniotomy and before radiographic evidence of tumor progression) had a higher rate of control compared to tumors that were treated at the time of radiographic progression following an initial observation period (P = .03). Similar results were reported by Harris et al[27] in their retrospective analysis of 30 aggressive meningiomas (combination of atypical and malignant lesions) treated with gamma knife radiosurgery. Therefore, we advocate early adjuvant radiotherapy of subtotally resected WHO grade II meningiomas. Finally, improved local control was seen with younger patients (age at treatment $\leq$60 years) (P = .01).

A potential disadvantage of omitting tumor bed irradiation is the risk of failure elsewhere inside the resection cavity (ie, regional failure). Little is known about which subset of patients with subtotally resected atypical meningioma would benefit from irradiation of the entire tumor bed. To answer this question, we examined the 20 radiation-naïve patients in our series. Of these, only 3 patients (patients 3, 4, and 5 from Table 3) had regional failures (ie, recurrence with a new tumor elsewhere in the resection bed). Therefore, one could argue that these 3 patients may have benefited from upfront tumor bed irradiation. However, even among this group, if the regional recurrence was not multifocal, salvage was achievable with repeat SRS (patients 3 and 5). Tumor bed irradiation should be considered for patients with multifocal recurrence.

It is doubtful that patients 1 and 2 would have benefited from resection tumor bed irradiation given that their treatment failed at the treated targets. Patient 1 eventually underwent external beam radiation at an outside institution. In hindsight, given that patient 1 presented with multifocal tumors, he may not have been an ideal candidate for SRS alone.

We have not routinely irradiated the entire tumor bed for patients presenting after STR of atypical meningiomas. Instead, we have treated only the residual tumor with SRS, after which patients are followed closely with serial imaging. Although the follow-up period is modest, the majority of patients in our series have done well, and importantly, have not required salvage larger volume cranial radiation. Thus far, SRS treatments have been well tolerated, and radiation toxicity has been observed in 2 (8%) of the 25 patients. However, a limitation of the present series is its length of follow-up. Additional toxicity may be encountered with time. A longer follow-up period is necessary to assess the long-term tumor control rate and to confirm safety. More studies are needed to identify the subset of patients who would benefit from tumor bed irradiation. Until then, one must weigh the risk of tumor bed recurrence with long-term neurocognitive effects of irradiating normal brain and tailor treatment recommendations to individual patients. In our experience of subtotally resected atypical meningiomas, early postoperative SRS to treat residual tumor decreases the risk of treatment failure. In addition, foregoing tumor bed irradiation in patients without multifocal disease can result in good local control. In cases of WHO grade II meningiomas treated with GTR, we offer close observation with consideration for SRS at the time of recurrence, with the goal of avoiding early and late side effects of large volume cranial irradiation. As with subtotally resected atypical meningiomas, more studies are needed.

CONCLUSIONS

The optimal adjuvant treatment for resected WHO grade II meningiomas has not been defined. Traditionally, irradiation of the entire tumor bed plus margin has been offered to decrease the risk of recurrence; however, the risk of late neurocognitive toxicity and impact on quality of life with such treatment must be considered in this group of patients with a prolonged life expectancy. Our experience with CyberKnife SRS in patients with subtotally resected WHO grade II meningiomas has shown that early irradiation is associated with lower risk of recurrence compared with waiting until tumor progression. Moreover, these data suggest that in radiation-naïve patients, a large subset of patients can achieve excellent clinical outcomes with SRS alone. More studies are needed to identify patients that may benefit from resection bed irradiation.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Over the past 2 decades it has been established that tumor histology is the most important factor associated with failed meningioma radiosurgery. In this article, Choi et al present the treatment results of CyberKnife radiosurgery for patients with atypical (WHO grade II) meningiomas. In reading through this article, there is a clear parallel between the authors decision making on radiation management and patient selection and what has evolved at our center. Specifically, patients who undergo a complete tumor removal documented on postoperative magnetic resonance imaging are followed with serial imaging for evidence of tumor recurrence and no form of radiation is recommended. Conversely, patients with tumor recurrence or residual tumor are recommended to receive radiosurgery with prescribed doses higher than used for benign meningiomas. The documented 3-year local tumor control rate (75%) in 20 patients managed with upfront radiosurgery illustrates the formidable challenge that patients with atypical meningiomas remain in our practice.

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