Gamma Knife Stereotactic Radiosurgery for Radiation-Induced Meningiomas

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Key Words

Gamma Knife • Stereotactic radiosurgery • Meningioma • Radiation-induced

failure of radiosurgery. **Conclusions:** Gamma Knife radiosurgery is both a safe and effective treatment for radiation-induced meningiomas.

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Abstract

Background: Radiation-induced meningiomas present a unique clinical dilemma given the fact that patients with these tumors have often received a prior full course of radiotherapy. As such, traditional radiotherapy is limited by lifetime tissue tolerances to radiation, leaving surgery and radiosurgery as attractive treatment options. **Objectives:** To ascertain the safety and efficacy of Gamma Knife radiosurgery as a treatment for radiation-induced meningiomas. **Methods:** A retrospective chart review was conducted to identify patients who received Gamma Knife radiosurgery for a meningioma and met the criteria for this being a radiation-induced tumor. Serial imaging was used to determine the outcome of treatment and clinical notes used to assess for toxicity. **Results:** We present our series of 12 patients with radiation-induced meningiomas treated with Gamma Knife stereotactic radiosurgery over a 12-year period at our institution. With a median follow-up of 35 months, local control was 100%. Two patients experienced distant brain failure (>2 cm from previous radiosurgical volume). Two patients experienced posttreatment toxicity related to treatment-related edema. A review of data collected from the scientific literature suggests that tumor volume predicts for treatment

Introduction

Radiation-induced meningiomas (RIM) are the most common radiation-induced neoplasms in the central nervous system [1–3]. As many as 20% of survivors of childhood brain radiotherapy develop RIM within 25 years of their original radiotherapy [4, 5]. Radiotherapy for benign disease such as tinea capitis has also been found to cause RIM [6]. RIM present a unique therapeutic dilemma given the complexity of re-irradiation and the tendencies for RIM to be high grade and multifocal [7, 8]. Surgery and stereotactic radiosurgery represent attractive treatment options for patients with RIM. However, surgery is not always an option for these patients if tumors are located in either surgically inaccessible regions or are multifocal. Outcomes of patients treated with radiosurgery for RIM are only just emerging given the relative rarity of this disease entity. To date, only two case series have described the efficacy and safety of stereotactic radiosurgery for RIM [9, 10].

The current report represents a single institution case series describing the use of Gamma Knife radiosurgery

Table 1. Characteristics of Kuhn et al.'s patients

Pa- tient No.	Age years/ sex	Reason for prior RT	RT dose Gy	Latency to SRS years	WHO grade	Meningioma location	Tumor volume cm ³	Margin dose Gy	Tumor status	Follow- up months	Toxicity grade – description
1	75/F	epidermoid carcinoma	66	7	NA	petroclival (R)	6.6	12	stable	138.5	3 – CN V, VII, VIII neuropathy
2	46/F	astrocytoma	NA	24	NA	petroclival (L)	0.91	13	stable	94.8	
3	43/F	medulloblastoma	45	18	NA	parasagittal (R)	1.97	18	stable	13	2 – left leg weakness and numbness
4	65/M	tinea capitis	NA	61	II	convexity (L)	1.8	18	stable	49.8	
5	53/F	astrocytoma	NA	28	II	convexity (R)	4.8	15	stable	6	
6	50/F	lymphoma	NA	39	II	cavernous sinus (R)	0.94	14	stable	6.9	
						convexity (L)	0.032	14	stable	6.9	
7	65/F	scalp hemangioma	NA	58	I	convexity (R)	9.3	12	stable	31.7	
8	51/M	oligodendroglioma	NA	38	NA	convexity (L)	0.93	12	stable	70.7	
9	46/M	neuroblastoma	NA	46	NA	tentorium (R)	1.6	13	stable	50.2	
10	39/M	ependymoma	NA	26	II	parasagittal	4.1	14	distant failure at 14.3 months	23.7	
						falcine (R)	0.96	14	stable	23.7	
						convexity (R)	0.17	14	stable	23.7	
						convexity (L)	0.16	14	stable	23.7	
						CPA (L)	0.19	14	stable	6	
						convexity (R)	1.85	15	stable	6	
						convexity (L)	0.15	15	stable	6	
11	73/F	pituitary tumor	NA	45	NA	sphenoid ridge (R)	1.4	13	stable	12.6	
						sphenoid ridge (R)	0.51	13	stable	12.6	
12	31/M	pilocytic astrocytoma	47.7	27	I	sphenoid ridge (R)	0.042	12	distant failure at 15.8 months	21.1	
						convexity (R)	0.98	12	stable	26.4	
						convexity (L)	0.071	12	stable	26.4	
						falcine	0.039	12	stable	26.4	
						falcine	0.14	12	stable	26.4	

RT = Radiotherapy; SRS = stereotactic radiosurgery; CN = cranial nerves; CPA = cerebellopontine angle.

(GKRS) in the treatment of RIM. We present the clinical outcomes including the patterns of failure and toxicities associated with treatment for a series of 12 patients treated with GKRS for RIM at Wake Forest Baptist Health between 1999 and 2011. We additionally review the literature on the treatment of RIM with radiosurgery in order to determine if any generalizations can be made from the larger data set regarding risk factors for treatment failure.

Methods

Patient Population

This study was approved by the Wake Forest Baptist Health Institutional Review Board. A total of 268 patients received GKRS for a meningioma between 1/1/1999 and 3/1/2011 at our institution. Of these, 12 (4.5%) met the previously described [10, 11] criteria for a RIM. The criteria used are as follows: (1) the tumor must develop within the field of prior irradiation; (2) a relatively long

period must elapse between the time of radiation and the time of tumor occurrence; (3) the tumor must be histologically distinct from the original tumor, and (4) the patient must not have a genetic predisposition toward tumor formation.

A summary of patient demographics, original indication for radiotherapy, latency since radiotherapy, and RIM characteristics can be found in table 1.

Radiosurgery Technique

After evaluation by a neurosurgeon and radiation oncologist, informed consent for GKRS was obtained. Placement of a four-pin Leksell stereotactic head frame was done under local anesthesia. After placement of the head frame, the patient underwent a high-resolution contrast-enhanced stereotactic MRI. A CT scan was obtained in place of an MRI in two patients. Radiosurgery treatment plans were generated using the Leksell GammaPlan treatment planning system (Elekta AB, Stockholm, Sweden) and executed using a Leksell model B or C GammaKnife unit (Elekta AB, Stockholm, Sweden). Median prescription dose prescribed to the margin of the enhancing tumor was 13.5 Gy (range 12–18 Gy).

Table 2. Common Terminology Criteria for Adverse Events grading criteria

Grade	Clinical characteristics
1	Asymptomatic or mild symptoms; intervention not indicated
2	Moderate; limiting activities of daily living; minimal, local, or noninvasive intervention indicated
3	Severe or medically significant; disabling; invasive intervention indicated
4	Life-threatening; urgent intervention required
5	Death related to adverse effect

Patient Follow-Up

Patients were followed clinically and with routine MRI. Patients generally underwent a posttreatment MRI 6 months after GKRS and then yearly thereafter. Local failure was determined as a tumor recurrence either within the prescription volume or within 2 cm of the tumor margin on MRI. Local failures were further divided into in-field failures (within the prescription isodose line) and marginal failures (within 2 cm of the prescription isodose line, but not contained within it). Distant failure was considered to be a failure that occurred beyond 2 cm from the prescription isodose line. Development of a new meningioma was considered a distant treatment failure. A treatment response was defined as a decrease in volume of the enhancing tumor. Toxicity was assessed using criteria as defined in the Common Terminology Criteria for Adverse Events (Version 4.0). Toxicity criteria are summarized in table 2.

Literature Search

A PubMed search (www.ncbi.nlm.nih.gov) was conducted using the search terms 'radiation' AND 'induced' AND 'meningioma', giving 45 results. The abstracts of each result were reviewed for patients with radiation-induced meningiomas that received stereotactic radiosurgery. Three publications met these criteria [9, 10, 12], and the data described in these articles were aggregated with our data (described above). The patient from Jensen et al. [10] who had a schwannoma of cranial nerve III was excluded from the aggregation since our report focuses exclusively on radiation-induced meningiomas. The relevant descriptive statistics for the aggregate data are shown in table 3. In total, there were 48 patients with 68 tumors treated with 54 instances of stereotactic radiosurgery. The original diagnoses were astrocytoma (n = 6), craniopharyngioma (n = 2), ependymoma (n = 2), epidermoid carcinoma (n = 1), esthesioneuroblastoma (n = 1), experimental (n = 1), glioma (n = 2), hemangioma of the scalp (n = 2), leukemia (n = 3), lymphoma (n = 1), medulloblastoma (n = 4), neuroblastoma (n = 2), oligodendroglioma (n = 3), pilocytic astrocytoma (n = 2), pineal mass (n = 1), pituitary adenoma (n = 8), retinoblastoma (n = 1), rhabdomyosarcoma (n = 1), spindle-cell tumor (n = 1), tinea capitis (n = 2), and unspecified (n = 2).

Table 3. Patient characteristics (n = 48)

Age at SRS, years	
Median	43.7
Range	12–75
Age at original RT, years	
Median	8.5
Range	0.3–68
Latency to SRS, years	
Median	28
Range	7–61
Sex, n	
Male	20 (41.7%)
Female	28 (58.3%)
WHO grade	
Unknown	28
I	12
II	8
Tumor location	
Convexity	21
Middle fossa	12
Sphenoid wing	8
Cavernous sinus	8
Falx	7
Parasagittal	5
Tentorium	2
Posterior fossa	2
Cribiform plate	1
Intraorbital	1
Tumor volume, cm ³	
Median	6.16
Range	0.0315–42.6
Margin dose, Gy	
Median	14
Range	5.4–20
Follow-up, months	
Jensen et al. [10] (n = 16)	
Median	37.2
Range	9.5–144.4
Kondziolka et al. [9] (n = 19)	
Median	34.5
Range	7–98
Kuhn et al. (n = 12)	
Median	26.4
Range	6–138.5
Galloway et al. [12] (n = 1)	57.6

SRS = Stereotactic radiosurgery; RT = radiotherapy.

Statistics

Local control and overall survival were estimated using the Kaplan-Meier method. A two-tailed Student's t test was used to determine differences between the populations that failed radiosurgery versus those that achieved local control.

Results

Survival

Overall survival was 100% at 1, 2, and 3 years. Cause-specific survival was also 100% at 1, 2, and 3 years. Disease-free survival was 100, 87.7, and 87.7% at 1, 2, and 3 years, respectively.

Patterns of Failure

Local control was 100% at 1, 2, and 3 years. Two treatment failures were observed, both at sites distant (>2 cm) from the radiosurgical site. The distant brain failure rate was 0, 12.3, and 12.3% at 1, 2, and 3 years, respectively. None of the failures were either within the radiosurgical volume or within 2 cm of the radiosurgical volume.

Toxicity

Two of 12 patients experienced adverse toxicity events after receiving GKRS. One patient developed neuropathy of cranial nerves V, VII, and VIII (grade 3) at 4 months post-GKRS. Another patient experienced left leg weakness and numbness (grade 2) at 3 months post-GKRS.

Analysis of the World Literature

A total of 48 patients with 68 tumors were identified using the 3 previously reported series of RIM and the current dataset. Univariate analysis using a two-tailed Student's *t* test was used to compare sizes of tumors between the cohort with progression-free survival and the cohort that experienced progression. It revealed that the median tumor size of tumors that failed treatment (median = 10.7 cm³) was larger than the median tumor size of tumors that were controlled (median = 2.2 cm³; *p* = 0.028). There was no significant difference between these two groups with respect to age, sex, or tumor grade.

Discussion

The first case of RIM was reported in 1953 by Mann et al. [13] in a pediatric patient who developed a RIM after having received curative radiotherapy for an optic glioma. Since that case, several populations of patients have been identified who have been prone to development of RIM. These risk populations include patients who receive radiotherapy for childhood cancer, atomic bomb survivors, and patients who received radiotherapy for tinea capitis. The latency between radiation exposure and development of a RIM can range from 2 to 63 years [8]. This latency depends on several factors and is generally short-

er in cases of higher radiation dose, larger volume of tissue irradiated, and younger age at exposure [8].

Approximately 24–38% of RIM have been reported to be atypical or malignant histology [7, 8]. While there is a wealth of evidence in the scientific literature for the treatment of incidentally discovered meningiomas with radiosurgery in the absence of pathology [14], there is also data to suggest that the treatment of patients with higher grade meningiomas with radiosurgery have worsened outcomes. Attia et al. [15] reported a series of WHO grade II meningiomas treated with radiosurgery and found a high rate of treatment failure within 2 cm of the radiosurgical volume. The authors additionally found that patients receiving greater than 14 Gy had improved freedom from progression.

Approximately 5–29% of RIM are multifocal [7, 8], and it is likely that the multifocality of these tumors is a result of field cancerization caused by the previous radiotherapy. In our current series, three of 12 patients had multifocal tumors at the time of radiosurgery. Two patients failed distantly from the initial radiosurgical site. The tendency for multifocality contributes to the complexity of the management of these patients. While repeat craniotomy is not necessarily contraindicated, it increases the complexity of an operation and time under general anesthesia. As such, radiosurgery provides a noninvasive alternative to multiple craniotomies in cases of multifocal tumors. Furthermore, because distant brain failure is a predominant mode of treatment failure after radiosurgery (12.3% at 1 year and 100% of treatment failures in the current series), the use of further radiosurgery for the development of new meningiomas is generally effective and quite tolerable to patients.

Two previous series of radiosurgery in the treatment of RIM have been reported. The University of Pittsburgh presented a series of 19 patients who received radiosurgery for RIM with a median margin dose of 13 Gy [9]. While overall survival at 5 years was high (81%), progression-free survival at 5 years was 67%. Two patients died of meningioma at the last follow-up. A series from the Mayo Clinic showed local control rates of 100% at 3 and 5 years in 16 patients treated for RIM with radiosurgery using a median margin dose of 16 Gy [10]. One patient died of malignant meningioma at just over 5 years from radiosurgery. The outcomes of these two series highlight two points: (1) RIM represent a heterogeneous population, which can contain higher grade meningiomas, and (2) these tumors are quite rare, and thus, the true patterns of failure of disease are unknown. As local control appeared to be somewhat better in the Mayo series, it may be advis-

able to treat RIM with doses used for grade II meningiomas in the absence of known pathology. Recent data from Attia et al. [15] suggest that appropriate doses for grade II meningiomas are >14 Gy to the tumor margin.

There are several limitations to this study. The total number of patients and tumors is small, making generalizations difficult or impossible. The ability to analyze the previously reported tumors within the scientific literature is also subject to bias given that the analysis is limited by only the factors that were reported in these reports.

Conclusion

Radiosurgery represents a feasible modality for treatment of RIM. Further studies are necessary to determine the patterns of failure of this rare disease entity.

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