The Effect of Radiation on Meningioma Volume Change

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■ BACKGROUND: **Radiation therapy is a common treatment for meningiomas. Volume changes of meningiomas in response to radiation are not well characterized. This study seeks to quantify the volume change of meningiomas following radiation.**

■ METHODS: **Data were collected from a retrospective single-institution database of cases from 2005–2015. Tumors were measured using T1-weighted post-contrast magnetic resonance imaging. Volumes were calculated using the ABC/2 ellipsoidal approximation.**

■ RESULTS: **A total of 63 patients fit the inclusion criteria; 37 patients (59%) received radiation following resection, 19 (30%) received radiation alone, 4 (6%) received radiation following a biopsy, and 3 (5%) had unknown surgical status. A total of 39 patients (62%) had skull base meningiomas; 43 tumors were World Health Organization (WHO) grade I, and 12 tumors were WHO grade II. Thirteen patients received radiosurgery, 43 received radiotherapy, and 7 received an unknown number of treatments. Eight patients did not attain local control and were excluded from volume analyses. WHO grade I meningiomas saw an average of 33% ± 19% decrease in tumor volume; WHO grade II tumor volumes decreased by an average 30% ± 23%. Radiosurgery saw an average volume decrease of 34% ± 13%, while radiotherapy resulted in volume decrease of 31% ± 21%. For those who achieved local control, there was an average decrease in tumor size of 30% ± 19%, 30% ± 22%, and 41% ± 19% over 0.5–1.5, 2.5–3.5, and >5 years, respectively.**

■ CONCLUSIONS: **Meningiomas treated with radiation exhibit nonlinear decrease in size over time. The greatest decrease in tumor volume occurs within the first year and begins to plateau 5 years post–radiation treatment.**

INTRODUCTION

Meningiomas are common intracranial tumors.[1-3] Although they are infrequently malignant, they often produce symptoms based on their size and location.[4] Surgical resection remains the primary treatment modality, but other forms of treatment are often warranted.[5]

Radiation plays a role both as adjuvant and occasionally as primary treatment for meningiomas.[6] It can be used following subtotal resection to improve control and following gross total resection to prevent recurrence in higher grade lesions. Long-term control rates following radiation for meningiomas are reported to average above 90%.[6-9] Despite the investigation of long-term control rates, long-term volume changes following radiation are not as well-characterized. Understanding tumor volume change is essential to understanding the long-term clinical impact of radiation.

There are several studies that have previously examined this question. Henzel et al. followed 84 patients who received fractionated stereotactic radiotherapy (FSRT) for up to 3 years and found a 36% reduction in tumor volume.[10] Astner et al. found a 30% reduction in tumor volume at 4–6 years in 59 patients that received FSRT or stereotactic radiosurgery (SRS) for skull base meningiomas.[11] This was the only study that included both SRS and FSRT but was focused solely on lesions at the skull base. Feigl et al. reported on 127 patients who underwent SRS and found a control rate of 96.4% with a mean tumor volume reduction of 46.1% over a mean follow-up time of 29.3 months.[12]

Key words
- Meningioma
- Radiation
- Radiosurgery
- Volumetrics

Abbreviations and Acronyms
3-D: 3-Dimensional
FSRT: Fractionated stereotactic radiotherapy
MRI: Magnetic resonance imaging
SRS: Stereotactic radiosurgery
WHO: World Health Organization

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This study was undertaken to further characterize the long-term effects of radiation on meningioma tumor volume with both FSRT and SRS regardless of location.

METHODS

Study Overview and Patient Selection

The data were collected from a retrospective brain tumor database populated at a single academic medical center for cases between January 2005 and February 2015. Within the sample of patients with brain tumors, those with tumors diagnosed as meningiomas were considered for inclusion in this study. Not all tumors had a tissue diagnosis; some only had a radiologic diagnosis of meningioma. The following inclusion criteria were used: (1) treatment with radiation; and (2) magnetic resonance imaging (MRI) scans available for analysis before and after radiation treatment. Criteria for exclusion were: (1) any patient who received another intervention following radiation (surgery or chemotherapy); (2) no MRI on record; (3) age less than 18 years; or (4) no details available for radiation treatment. All radiosurgery was performed using a linear accelerator.

Patient demographics (age, sex), tumor characteristics (months of follow-up, number of images, number of tumors, location), treatment characteristics (radiotherapy or radiosurgery), and MRI features (tumor diameters and volume) were collected for each patient. Institutional review board approval was secured for the study protocol.

Image Review and Tumor Volume Measurement

Tumor volume was determined from T1-weighted post-gadolinium MRI images. Tumor volumes were measured using 3 orthogonal axes. In the axial plane, the largest diameter (A) was measured, followed by its largest perpendicular (B). The vertical diameter (C) was obtained from the sagittal plane. The larger of A or C was used as the largest linear diameter. The simplified ellipsoid volume (ABC/2) for each tumor was calculated from the 3 orthogonal diameters, as in Figure 1. It has been previously demonstrated that volumes of intracranial lesions derived from the ABC/2 method correlate well with planimetric techniques.[13-17]

Tumor Grade Assignment

In order to evaluate the role of tumor grade in meningioma response to radiation, the grade assigned to the tumor at the time of prior surgery was used for those tumors for which this information was available (37 patients). The remaining 26 unoperated patients were assigned tumor grade based on MRI characteristics. Indeed, all of these unoperated tumors were assigned a grade of 1 as they were homogeneously enhancing lesions with dural tails and without

Figure 1. T1-weighted post-gadolinium magnetic resonance images demonstrate how to measure the A, B, and C dimensions to calculate the simplified ellipsoidal volume. On the left image, A is the longest dimension measured in the axial plane, with B being the longest perpendicular dimension to A in the same axial cut. On the right image, C is longest dimension orthogonal to A in the sagittal plane.

features associated with higher grade: cystic components, extension through cranial foramina, significant lobulations, flow voids, or substantial peritumoral edema. The latter features have previously been shown to correlate with higher-grade meningiomas.[18,19]

Analysis

Demographic and tumor information for patients fulfilling inclusion criteria were summarized using means and standard deviations or frequencies and percentages. Details of treatment prior to radiation were collected, as well as the rationale for radiation. Patients were separated by groups according to tumor histopathology and whether they received SRS or FSRT. Radiosurgery was classified as 5 or fewer fractions of radiation, as defined by the 2006 consensus statement of the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the American Society for Therapeutic Radiology and Oncology.[20] Additional subgroup analysis was conducted on those lesions where MIB-1 indices were reported. Length of follow-up after radiation was calculated based on date of radiation and latest available MRI. The change in size of tumor was calculated by determining both absolute volume change and relative percent volume change.

A criterion of $P < 0.05$ was used to determine statistical significance. We conducted t tests for quantitative variables and analysis of variance testing was used for qualitative variables. All calculations and data analyses were conducted in Excel 2016 (Microsoft Corp., Redmond, WA).

RESULTS

Demographics

A total of 115 patients met inclusion criteria; after applying exclusion criteria, however, 63 patients remained. There were 48 female and 15 male patients. The mean age at the initiation of radiation was 54.9 years (range: 22.8–87.1 years). A total of 37 patients received prior surgical resection; 39 of the lesions were located at the skull base. Mean initial tumor volume prior to radiation was 5.1 mL (range: 0.04–49.85 mL). These results are presented in Table 1.

Table 1. Demographics and Tumor Characteristics

Variable	Value
Mean age, years	54.9 (22.8–87.1)
Sex	
Female	48 (76%)
Male	15 (24%)
Location	
Skull base	39 (62%)
Other	24 (38%)
Prior intervention	
Resection	37 (59%)
Biopsy	4 (6%)
None	19 (30%)
Unknown	3 (5%)
Initial volume, mL	5.1 (0.04–49.85)
WHO grade	
I	49 (78%)
II	14 (22%)

Values are presented as mean (range) or n (%).

Responsive versus Nonresponsive Groups

Thirteen percent (n = 8) of patients had growth of their meningiomas after radiation, and were termed radiation nonresponders. There was no significant difference in age, tumor grade, or follow-up time between patients with tumors that grew after radiation and those with tumors that did not. These results are presented in Table 2. The average increase in tumor volume for patients that did not achieve local control was 106% (range: 4%–241%). Among the remaining patients, termed radiation responders, tumors showed decrease in volume over time, and subsequently attained stable, smaller volumes that did not further decrease.

Treatment Details and Tumor Response

SRS was administered to 13 and FSRT to 43 patients; the number of fractions was not available for 7 patients. The average dose was 18.1 Gy for SRS and 52.2 Gy for FSRT. In the SRS group, 11 patients received only 1 fraction. The mean relative decrease in tumor volume for all 55 patients where control was achieved was 32% with an average follow-up time of 4.27 years.

Among the radiation responders, there were 43 with World Health Organization (WHO) grade I lesions and 12 with grade II lesions. There was no significant difference in mean initial tumor volume, mean absolute decrease, mean percentage decrease, or length of follow-up between the grade I and grade II lesions. These results are presented in Table 3.

In comparing the SRS group to the FSRT group, there was no significant difference between mean initial tumor volume, mean absolute decrease, mean percentage decrease, or length of follow-up. These results are also presented in Table 3.

In the subset of patients with MIB-1 staining index, there were 20 with an index ≤5% and 7 with an index >5%. Between these 2

Table 2. Comparison of Radiation Nonresponders to Radiation Responders

Parameter	Nonresponders (n = 8)	Responders (n = 55)	*P* Value
Age, years	49.7 ± 18.7	54.9 ± 13.9	0.375
Male/Female	3 Male/5 Female 62.5% Female	12/43 78.2% Female	0.382
Grade I/Grade II	6 Grade I/2 Grade II 25% Grade II	43/12 22% Grade II	1.000
Overall follow-up time, years	3.85 ± 4.79	3.30 ± 3.16	0.774

Values are presented as mean ± standard deviation or n (%).

Table 3. Comparisons Among WHO Grade, SRS Versus FSRT, MIB-1 Staining, Tumor Location, Previous Treatment, and Length of Follow-up

Variable	Mean Initial Tumor Volume (mL)	Mean Absolute Decrease in Tumor Volume (mL)	Mean Relative Decrease in Tumor Volume (%)	Number of Patients
WHO Grade I	5.40 ± 8.60	1.29 ± 1.59	33 ± 19	43
WHO Grade II	3.11 ± 8.90	0.53 ± 0.71	30 ± 23	12
	$P = 0.462$	$P = 0.054$	$P = 0.385$	–
SRS	2.55 ± 9.05	0.84 ± 0.94	34 ± 13	11
FSRT	5.61 ± 8.95	1.10 ± 1.60	31 ± 21	39
	$P = 0.347$	$P = 0.334$	$P = 0.996$	–
MIB-1 ≤ 5%	3.68 ± 9.15	1.10 ± 1.54	34 ± 19	19
MIB-1 > 5%	3.44 ± 9.15	0.30 ± 0.43	29 ± 24	7
	$P = 0.767$	$P = 0.157$	$P = 0.107$	–
Skull base	4.28 ± 4.30	1.26 ± 1.43	33 ± 19	38
Convexity	6.36 ± 14.55	1.39 ± 2.00	37 ± 18	11
Multiple	3.71 ± 1.88	0.98 ± 0.99	24 ± 15	3
	$P = 0.706$	$P = 0.918$	$P = 0.559$	–
Surgery	3.54 ± 3.97	0.98 ± 1.31	31 ± 18	32
Biopsy	8.10 ± 6.04	2.52 ± 1.77	36 ± 20	4
None	5.84 ± 11.59	1.47 ± 1.70	39 ± 18	17
	$P = 0.371$	$P = 0.121$	$P = 0.397$	–
Overall change	4.90 ± 4.31	1.30 ± 1.33	32 ± 19	–
0.5—2 years of follow-up	6.16 ± 11.9	1.30 ± 2.02	30 ± 19	–
2—5 years of follow-up	4.53 ± 5.2	0.99 ± 0.99	30 ± 22	–
>5 years of follow-up	3.24 ± 1.83	1.29 ± 1.07	41 ± 19	–
P value	0.633	0.990	0.123	–

groups, there was no significant difference between mean initial tumor volume, mean absolute decrease, mean percentage decrease or length of follow-up. These results are additionally presented in Table 3.

The location of meningiomas in those radiation responders included 38 tumors at the skull base, 11 at the convexity, and 3 in multiple locations. There was no significant difference in mean percentage or absolute decrease in tumor volumes based on meningioma location. These findings are shown in Table 3.

In our cohort, 32 patients had prior meningioma treatment with surgery, 4 had a prior biopsy, 17 had no prior treatment documented, and 2 had unknown prior treatments. When analyzing prior treatment modalities for meningioma patients, we found no significant difference in mean absolute decrease or mean percentage decrease of tumor volume. These results are demonstrated in Table 3, as well.

Figure 2A presents the amount of tumor volume change by initial volume. This demonstrates that there is no significant correlation between initial tumor volume and percentage decrease.

The analysis of tumors by length of follow-up after radiation demonstrated that tumors exhibit a continued decrease up to 5 years of follow-up. These results are presented in Table 3.

Figure 2B is a graphic displaying the volume remaining as a percentage over time. Data are displayed with error bars that represent ±1 standard deviation. On average, the remaining tumor volume approaches an asymptote of about 60% volume remaining after 5 years of follow-up. The greatest decrease in tumor volume occurs in the first year after treatment and progressively decreases until it reaches this asymptote. Between grade I and grade II tumors, grade II tumors exhibited greater variation in response to radiation, with a range of −24% to 78% volume remaining and a standard deviation of 28%. Response of grade I tumors in this sample ranged from −16% to 60% volume remaining with a standard deviation of 20%.

DISCUSSION

Neurosurgeons are often called upon to counsel patients with difficult-to-resect meningiomas or with recurrent growth after resection. These discussions invariably involve the expected outcomes from radiation and the factors that may influence those outcomes. We have addressed the questions of what percentage of meningiomas respond to radiation, how meningioma volume

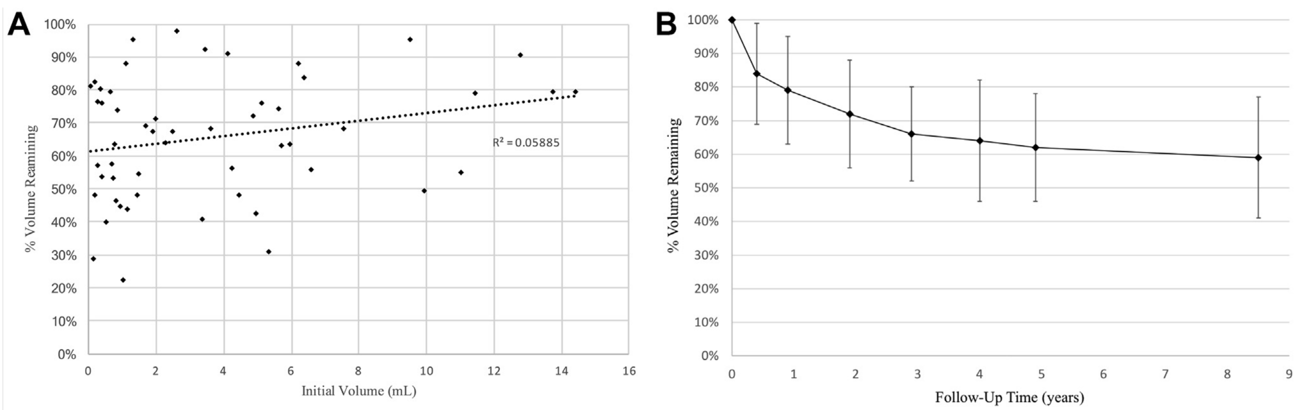

Figure 2. (**A**) Percent meningioma volume remaining based on initial tumor volume for each individual patient. (**B**) Average percent of meningioma volume remaining over follow-up time in years.

changes over time in response to radiation, whether meningioma characteristics such as size, grade, MIB-1 staining index, tumor location, or prior tumor treatment affect response, and whether there is a difference in response between radiosurgery and radiotherapy. Additionally, we have looked to see if there is a difference in patient and tumor characteristics among those who did and did not respond to radiation.

In line with previously reported results, 87.3% of meningiomas in this series exhibited a response to radiation. Patient age, sex, follow-up time, and tumor grade did not differ between radiation responsive and non-responsive tumors. Further studies with larger sample sizes should aim to characterize what factors influence meningioma response to radiation.

The results presented here support the hypothesis that meningioma response to radiation is greatest in the initial period but that the rate of shrinkage declines to zero after 1–3 years.

This study provides evidence that meningioma volume decreases nonlinearly over time in response to radiation, with 50% or more of the volume change occurring within the first year following radiation. Figure 2B demonstrates the decreasing rate of volume change and indicates that the average relative tumor volume reduction in our sample approaches an asymptote at about 60% volume after several years. Among radiation responders, although each tumor demonstrates differing degrees of response, further analysis of these data suggests that mathematical modeling of individual tumor volumes over time allows accurate prediction of the final asymptotic volumes of the tumors that have been treated (unpublished data).

These results suggest that there are many factors that do not appear to affect meningioma response to radiation, though the power of these findings is limited. Sex and age at the beginning of radiation treatment are not correlated, which is supported by Astner et al.[11] Nor is initial tumor volume, WHO grade, MIB-1 staining index, or the modality of radiation, which is supported by Han et al.[21] There also was no evidence suggesting either prior meningioma treatment or meningioma location were associated with tumor response to radiation.

Limitations

There are several limitations to this study: the sample size, the retrospective design, the method of volume measurement, and the time elapsed between initial MRI and start of radiation. Sixty-three patients were eligible for inclusion and 55 responded to radiation, which left only small sample sizes for subgroup analyses. Given these small sample sizes, the results from this study warrant further evaluation with larger sample sizes and longer follow-up to continue to assess factors that influence meningioma response to radiation.

It is important to be mindful of the ellipsoid volume estimation (ABC/2) of meningioma volume, and it is certainly a valid criticism. It is known that this may not accurately reflect the volume of irregularly shaped tumors, which can often be assessed more accurately with a volumetric 3-dimensional (3-D) technique. However, the nature of this retrospective study made it such that many of the scans to be evaluated were not amenable to the 3-D volumetric methodology. Moreover, we have found in a previous series of meningioma volume measurements that the ABC/2 method provides surprisingly consistent volumes in correlation with a 3-D volumetric technique.[14] Moreover, sequential measurements of each tumor in the same patient over time were carried out using dimensions with the same orientations for each time point. Thus, any inaccuracy of the ABC/2 method for estimating volume related to irregular tumor shape should have resulted in a reproducible error for each time point, allowing for relatively accurate comparisons and assessment of volume changes over time following radiation exposure. Volumetric measurement software is also not available to all clinicians; thus, the simplified ellipsoid approximation may be more widely applicable in allowing clinicians to counsel patients and predict tumor volume changes following radiation.

The time elapsed between the MRI used to measure the initial tumor volume and the start of radiation treatment may have posed a potential source of error as well. The greater this period is, the larger the tumor may grow before receiving radiation. The greatest amount of time elapsed between initial MRI and start of radiation was 4 months, however—making it unlikely that this would have been a confounder in this study.

Histologic subtypes and molecular genetics were not widely available in this sample, unfortunately. Future analyses evaluating the effect of histological and molecular subtypes on radiation response and volume change would be valuable.

CONCLUSIONS

Meningiomas are common intracranial tumors that can be treated with radiation. This study provides evidence that the majority of these tumors are radiation responders and that meningioma volumes decrease nonlinearly in size over time in response to radiation. These tumors appear to approach an asymptotic plateau after several years. For radiation-responsive meningiomas, the largest portion of volume loss occurs over the first year and thereafter approaches a plateau of 60% of initial volume. There was no appreciable difference in volume shrinkage by sex, age, FSRT versus SRS, WHO grade I versus WHO grade II lesions, tumor location, prior treatment modality, MIB-1 staining index, or initial volume. This study aids clinicians in counseling patients with growing or recurrent meningiomas on the likelihood of responsiveness to radiation as well as the expected extent of response.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Jacob T. Hall: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Charles F. Opalak:** Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Matthew T. Carr:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Timothy J. Harris:** Conceptualization. **William C. Broaddus:** Conceptualization, Writing – original draft, Writing – review & editing.

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