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ORIGINAL ARTICLE

Stereotactic radiosurgery in patients with multiple intracranial meningiomas

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Summary

Purpose: *Stereotactic radiosurgery (SRS) delivers a potent, highly focused dose of radiation to the tumor while sparing the surrounding normal tissues. The purpose of this study was to assess the outcome of patients with intracranial meningiomas treated with SRS.*

Methods: *A total of 73 patients with 221 benign meningiomas treated between 1991 and 2005 with SRS and followed up for more than a year were reviewed. Fifty patients (68%) were treated with SRS to the primary meningioma while 23 (32%) received SRS to relapsing tumors adjacent or distant from the site of the initial meningioma that was previously treated with surgery alone. Mean tumor margin dose was 14 Gy (range 10-16). SRS was delivered after surgery in 117 meningiomas (55 patients).*

Results: *The median age at diagnosis was 47 years (range 16-74) and the median follow-up 5.8 years (range 1-13.6). The 3- and 5-year overall survival (OS) rates for all patients were 95% and 90%, respectively. The mean gross tumor volume decreased from 4.17 cm^3 to 3.23 cm^3 after SRS (p=0.057). Twenty-two (10%) meningiomas increased after SRS. In addition, clinical symptoms improved in 36% and remained stable in 45% of the patients. With regard to morbidity of SRS, only 7 patients (9.6%) had late complications, including edema (N=4), brain necrosis (N=4), gliosis (N=1), and paresis of the III pair nerve (N=1). There was no treatment-related mortality.*

Conclusion: *SRS for patients with multiple intracranial meningiomas is effective yielding a high rate of local tumor control, whereas treatment-related morbidity remains low.*

Key words: *brain tumor, meningioma, outcome, stereotactic radiosurgery*

Introduction

Meningiomas are common tumors of the central nervous system that originate from the meningeal coverings of the spinal cord and the brain. They account for up to 30% of all primary brain tumors in adults with a predominance in females, and an incidence of 4.5 per 100,000 person-years [1]. The incidence of meningiomas is climbing, which may indicate more sensitive diagnostic modalities or increased exposure to environmental risk factors [2]. Despite their benign histology, intracranial meningiomas may lead to substantial morbidity, due to the tumors themselves and/or from treatment, especially in those cases with multiple meningiomas which may require several therapeutic interventions throughout life [3].

Optimal management of meningiomas has been controversial and includes observation, surgical tumor removal, tumor resection with adjuvant radiotherapy, and radiotherapy alone. Many authors recommend treatment in patients with progression of symptoms and/or tumors close to critical structures [4,5]. Even though advances in surgical approaches have greatly improved patient outcomes for meningiomas once thought to be unresectable, long-term disease-free survival remains a desirable but elusive goal [6]. For example, tumor resection (Simpson grades 1-2) is

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achieved in only 20-87.5% of patients with meningiomas located at the skull base [7]. In addition, postoperative complications occur in 16-61% of patients, although overall complication rates are not always reported [7]. Therefore, SRS, the delivery of a high, single dose of radiation to a discrete tumor volume, is increasingly accepted as an alternative to conventional surgery in selected patients [8,9]. Stereotactic-guided radiotherapy is able to target surgically inaccessible or difficult lesions and has decreased risk of complications related to surgery and anesthesia [6,10-12].

Studies by our team [13] and others [7,14] have reported the benefit of stereotactic-guided radiotherapy in meningiomas that are close to critical structures, such as cranial nerves and the carotid artery. However, whether the outcome of patients with multiple meningiomas is similar remains unclear. We performed a review of patients with multiple intracranial meningiomas from our institution treated with SRS with the goal of assessing tumor response, symptom control, and treatment-related morbidity.

Methods

Patient population

The institutional review board approved a retrospective chart review, which was conducted for individuals with multiple (≥2) intracranial meningomas treated with SRS. We identified 73 patients from 1991 to 2005. Six cases (8%) were associated with type 2 neurofibromatosis. The standard patient evaluation included history and physical examination, computed tomography (CT) and/or magnetic resonance imaging (MRI) scan. Before the treatment of any patient, informed consent was obtained. Patients were followed up every 3-6 months after therapy for 2 years and at least once yearly thereafter. The follow up evaluations consisted of a history and physical examination and CT/MRI scans were obtained at intervals of 6-12 months or more frequently if clinically indicated.

Inclusion criteria and treatment

The criteria for performing SRS were: 1) tumor residuals or relapse(s) after surgical management; 2) fast-growing tumors; 3) tumor growth causing symptoms; 4) re-irradiation was considered, when keeping the above criteria.

SRS was performed with linear accelerator (LINAC), using 6 MV photons with a high-precision positioning system with mechanical fixation of the tertiary collimator (SRS200-University of Florida). To locate the lesions, MRI images were obtained on the day of SRS, subsequently placing under local anaesthesia the stereotactic frame and performing the planning CT. To establish the planning tumor volume, an automatic imaging fusion program was used. Treatment planning was performed in 3D in all cases, but using several treatment planning software platforms during the study period (BRAIN LAB, PLATO-Nucleotron, ERGO-3D Line and Pinacle-ADAC). After performing SRS, all patients received one day prophylaxis with dexamethasone and stayed at the hospital for 24 hours. Median tumor margin dose delivered was 14 Gy (range 10-16).

Response evaluation

The response was evaluated by CT scan or MRI 1-3 months after completion of SRS. The criteria used to determine objective tumor response for target lesions have been adapted from the original WHO Handbook and were recorded as follows [15]: complete response (CR) - defined as disappearance of the target lesion; partial response (PR) - defined as at least 30% decrease in the longest diameter of the target lesion, taking as reference the baseline longest diameter; progressive disease (PD) - at least a 20% increase in the longest diameter of the target lesion, taking as reference the smallest longest diameter recorded since the treatment started; stable disease (SD) - neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the reference size being the smallest longest diameter since the start of treatment [16].

Statistics

All data analyses were done using the SPSS (version 19.0) statistical software. The Kaplan-Meier [17] product-limit method provided estimates of OS. OS was defined as the interval between the first SRS date to the date of death from any cause or the last date of follow up for censored patients. Non-parametric analysis (Mann–Whitney and Wilcoxon tests) were performed for comparisons. A p-value less than 0.05 was considered statistically significant.

Results

The median follow-up time from the first SRS was 5.3 years (range 1-13.6). Patient characteristics are shown in Table 1. The median age at diagnosis was 47 years (range 16-74). Fifty patients (68%) were treated with SRS to the primary meningioma, and 23 (32%) patients received SRS to relapses adjacent or distant from the site of the initial meningioma that was previously treated with surgery alone (Table 1). A total of 221 meningiomas (range per patient 1-10; Table 2) underwent SRS. SRS was delivered after surgery in 117 meningiomas (N=55). The 3- and 5-year OS was 95% and 90.5% respectively.

Table 1. Characteristics of patients treated for multiple meningiomas

Characteristics	*No. of patients (N=73) N (%)*
Age (years)	
Median (range)	47 (16-74)
Gender	
Female	50 (69)
Male	23 (32)
Neurological deficits before SRS	
Yes	51 (70)
No	22 (30)
Relapse after prior surgery	
Yes*	23 (32)
No	50 (68)
Treatment[a]	
Surgery+SRS[b]	55 (75)
SRS[c]	18 (25)
SRS dose (Gy)	
Median (range)	14 (10-16)
Pre-SRS tumor volume (cc)	
Median (range)	4.2 (0.04-42)
Post-SRS tumor volume (cc)	
Median (range)	3.2 (0-43)

SRS: stereotactic radiosurgery. *47 relapses were treated in 23 patients. Five out of 23 patients also underwent surgery+SRS for other lesions. a: 221 meningiomas were treated in 73 patients. b: 117 meningiomas were treated with surgery+SRS. c: 104 meningiomas were treated with SRS alone

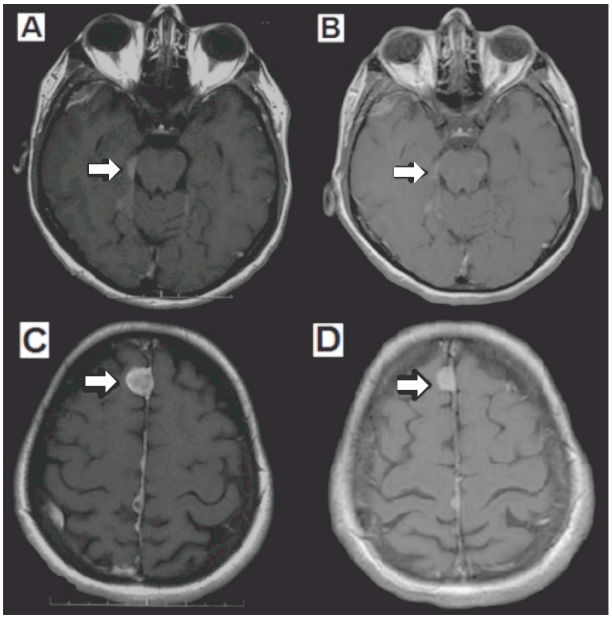

Figure 1. Gadolinium-enhanced T1-weighted magnetic resonance imaging immediately before (**A,C**; arrows) and 2 years after stereotactic radiosurgery (**B,D**; arrows) for two meningiomas in the same patient.

Table 2. Number of stereotactic radiosurgeries (SRSs) per patient

No. of SRSs	*No. of patients (%)*
1	16 (22)
2	32 (44)
3	7 (10)
4	5 (7)
5	6 (8)
6	1 (1)
7	3 (4)
8	1 (1)
9	1 (1)
10	1 (1)

Table 3. Summary of most common presenting neurological deficits in 51 patients who underwent stereotactic radiosurgery (SRS) for meningiomas

Pre-SRS neurological deficit	*No. of patients* (%)*
Visual dysfunction	12 (16)
Cerebellar disorders	11 (15)
Hemiparesis/Hemiplegia	10 (14)
Generalized muscle weakness	17 (23)
Cranial nerve deficits	28 (38)
Migraine	15 (21)
Seizure	20 (27)

*Patients had multiple meningiomas and presented with several neurological deficits

Response to treatment

The mean gross tumor volume decreased from 4.2 cm^3 (range 0.04-42) to 3.2 cm^3 (range 0-43) after SRS (p=0.057). Fifty-seven percent of meningiomas treated with SRS showed CR or PR after treatment (Figure 1), 33% (N=72) remained stable, and 10% (N=22) increased. Surgery was required in 8 (3.6%) meningiomas after SRS.

Clinical outcome

Fifty-one patients (70%) had neurological symptoms before SRS. The most common presenting neurological deficit was cranial nerve deficit (38% of the cases; Table 3). Clinical improvement was defined as resolution of neurological or cranial nerve deficits, or a reduction of preoperative symptoms. Neurological status improved in 27 (37%) patients, remained stable in 33 (45%), and deteriorated in 13 (18%). In addition, 10 (14%) patients underwent a short course of oral corticosteroid therapy, and 37 (51%) required long-term anti-convulsive therapy. Only 7 patients (9.6%) experienced late (>6 months) toxicity after SRS, including brain

edema (N=2), brain necrosis (N=2), both edema and brain necrosis (N=1), gliosis (N=1), and paresis of the cranial nerve III pair (N=1). No patient experienced grade 5 toxic effects.

Discussion

SRS uses exceptionally precise, focused radiation beams to treat tumors and other abnormal growths. Advantages of SRS include relatively low costs and high accessibility. The pertinent findings of this study can be summarized as follows. First, patients with meningiomas treated with SRS showed a good tumor response. Mean gross tumor volume decreased after SRS with a marginal statistical significance. Second, excellent OS rates were observed. Third, SRS was well tolerated in almost all patients with minimal incidence of late toxicity. Finally, there was a clinical improvement or stabilisation in the majority of patients.

The clinical benefit (CR, PR, and SD) in this series was 90%. This rate is comparable to other published radiosurgery series [18,19]. Pollock et al. [18] retrospectively reviewed 251 patients subjected to SRS for imaging-defined intracranial meningiomas between 1990 and 2008. The authors reported that on radiographic follow-up 72% and 27% of tumors became smaller or remained unchanged in size, respectively. In contrast to our findings, only 1.2% had in-field tumor progression after radiosurgery compared with 10% in our series. Several potential reasons may explain this divergence. The study from Rochester [18] excluded patients having prior surgery and patients with neurofibromatosis. In addition, 32% of the patients in our study were relapsing cases while the study by Pollock et al. [18] excluded these patients.

In regard to the second finding that OS rates exceeded 90% at 5 years, our findings are consistent with reports of other authors [20,21]. Stafford et al. [21] reported the outcome of 190 consecutive patients with 206 meningiomas who underwent SRS. The median tumor margin dose was 16 Gy and the median clinical follow-up period was 47 months. The cause-specific survival rates at 5 and 7 years were 94 and 92%, respectively. The University of Pittsburgh Cancer Institute [20] evaluated the outcome of 73 patients with meningioma (median volume 5.5 cm^3) who underwent stereotactic-guided radiotherapy. Treatment consisted of a median dose of 17.5 Gy and follow-up ranged from 1.5 to 98 months (median 16). At the time of the last follow-up, 51 of the 73 (70%) patients were alive with disease, 12 (16%) were alive without disease, 6 (8%) had died of disease, and 4 (6%) had died of other causes.

With respect to the clinical outcome, the majority of patients experienced neurologic improvement or stabilization. Our findings are consistent with other previously published studies [22-24]. For instance, Han et al. [23] reported 45% rate of cranial neuropathy improvement in patients with skull base meningiomas who had cranial neuropathy before radiosurgery. Iwai et al. [24] reported rates of clinical improvement similar to ours. Neurological status improved or remained stable in 65% of the patients. In addition, Majdoub et al. [22] reported the outcome of 78 patients with 87 intracranial meningiomas who were treated with LINAC radiosurgery, either as a primary or salvage treatment following one or more microsurgical procedures. After a median follow-up of 80 months, 24 (34%) patients showed improved clinical status (paresis of nevus abducens 18/48, facial paresis 4/8, and hemiparesis 2/9) and 41 (59%) patients remained stable.

In terms of late side effects, only 7 (9.6%) in our series experienced late toxicity. The low rate of chronic toxicity observed is consistent with other published studies [18,24]. For example, Osaka City General Hospital [24] reported the outcome of 108 patients with benign cranial base meningiomas treated with radiosurgery. The median dose delivered to the tumor margin was 12 Gy and the tumor volumes ranged from 1.7 to 55 cm^3 (median 8). Adverse effects of radiation were observed in 9 patients. There was permanent injury in 7 (6%) patients and transient injury in 2 (2%). The transient radiation injuries included temporal lobe edema and seizure, while the permanent injuries included facial spasms, temporal lobe edema, worsening of a preexisting oculomotor nerve, hemiparesis, worsening of tinnitus, and vertigo.

Except the inherent constraints in any retrospective analysis, our study has several limitations. First, there were inherent methodological study shortcomings that affected the applicability of the findings, such as the inclusion of different intracranial tumor locations. Second, the study period was long and the population was heterogeneous in terms of both tumor factors and treatment factors. As noted above, differences in type of treatment (postoperative SRS vs SRS alone) and disease status (primary tumors vs relapses) may have confounded our findings, although the magnitude of this effect is unclear. Prospective studies with similar baseline characteristics among groups are needed to better understand the role of SRS in each scenario. Finally, although we assessed the neurologic symptom control after SRS, other parameters

such as the quality of life or the preservation of neurocognitive function would be needed to better understand the impact of SRS. Previous studies suggest that radiosurgical patients may experience higher quality of life than surgical patients, especially in the short-term, because radiosurgery is a minimally invasive outpatient procedure [25-27].

Notwithstanding these limitations, our study provides data on the impact on SRS in patients with multiple intracranial meningiomas. Our findings show that SRS for intracranial meningiomas is effective, yielding a high rate of local tumor control, whereas treatment-related morbidity remains low. Multicenter studies with larger sample of patients treated with different SRS techniques (i.e. Cyberknife) may allow to expand our current results and create an algorithm for evaluating the most appropriate SRS treatment for intracranial meningiomas based on tumor factors (size, location) or patient preferences (frameless vs frame-based treatments).

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