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Stereotactic radiosurgery boost to the resection cavity for cerebral metastases: Report of overall survival, complications, and corticosteroid protocol

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Abstract

Background: This report focuses on the overall survival and complications associated with treatment of cerebral metastases with surgical resection followed by stereotactic radiosurgery (SRS). Management and complications of corticosteroid therapy are underreported in the literature but represent an important source of morbidity for patients.

Methods: Fifty-nine consecutive patients underwent surgical resection of a cerebral metastasis followed by SRS to the cavity. Patient charts were reviewed retrospectively to ascertain overall survival, local control, surgical complications, SRS complications, and corticosteroid complications.

Results: Our mean follow-up was 14.4 months (median 12.0 months, range 0.9-62.9 months). Median overall survival in this series was 15.25 months and local control was 98.3%. There was a statistically significant survival benefit conferred by Radiation Therapy Oncology Group recursive partitioning analysis Classes 1 and 2. The surgical complication rate was 6.8% while the SRS complication rate was 2.4%. Corticosteroid complications are reported and dependence at 1 month was 20.3%, at 3 months 6.8%, at 6 months 1.7%, and at 12 months no patients remained on corticosteroid therapy.

Conclusions: Overall survival and local control with this treatment paradigm compare well to the other published literature. Complications associated with this patient population are low. A corticosteroid tapering protocol is proposed and demonstrated lower rates of steroid-related complications and dependence than previously reported.

Key Words: Cerebral metastases, corticosteroids, stereotactic radiosurgery

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INTRODUCTION

Cerebral metastasis is the most common intracranial tumor in the adult population and the incidence is rising.[28] As many as 40% of cancer patients will develop cerebral metastases during their disease course;[7] this,

combined with enhanced detection capabilities and cancer therapies that extend overall life expectancy, makes the treatment of cerebral metastases an important consideration in modern cancer therapy.[28]

Historically, cerebral metastases were managed with palliative therapy and were considered the end stage of a patient's disease.[32] This improved with the introduction of corticosteroid therapy in the 1960s[8] and improved again with the subsequent addition of whole brain radiation therapy (WBRT).[33] Currently, management consists of a combination of surgery, WBRT, and stereotactic radiosurgery (SRS), and the specific regimen is tailored to each patient and the preferences of the treating physician.[3,34-36] There is evidence that surgical resection followed by SRS to the resection cavity may provide superior local control rates as compared with standard therapy, notwithstanding a higher rate of distant recurrence.[17,22,31,38] Recent interest has focused on the utility of SRS for patients with oligometastatic disease.[37,42]

Corticosteroid use for the management of symptomatic peritumoral edema is a mainstay of treatment.[40] Dexamethasone is the most commonly chosen agent given its potent anti-inflammatory properties and lack of mineralocorticoid activity.[4] However, corticosteroids can have harmful side effects such as hyperglycemia, Cushing's syndrome, psychiatric symptoms, osteoporosis, and steroid myopathy among others.[40] These side effects represent a significant source of morbidity. Hyperglycemia, for example, has been associated with decreased overall survival when it persists greater than 3 months after surgical resection.[26] Weissman *et al.* found that 51% (30/59) of patients suffered at least one steroid toxicity and 19% (11/59) were hospitalized secondary to corticosteroid-related complications.[52] Current recommendations regarding the termination of corticosteroid therapy state only that the agent should be tapered over a 2 week period or longer if clinically indicated.[41]

The present study examines the overall survival and complications for patients with cerebral metastases treated by surgical resection followed by SRS to the cavity. We also propose a protocol for the management of corticosteroid therapy in this population.

MATERIALS AND METHODS

During a 2-year period from 2010 to 2012, 59 consecutive patients who underwent surgical resection of a cerebral metastasis followed by SRS to the resection cavity were identified. This time period was selected because it represents the initiation of this protocol to the start of the study period. Metastatic lesions at our institution are treated exclusively by the two senior authors (LM and AD) and the cases selected were identified from a prospectively maintained database.

Patient information was obtained from the hospital chart and outpatient records from the Departments of Neurosurgery, Oncology, and Radiation Oncology. This work was conducted as part of studies approved by the institutional review board at Rush University Medical Center (Chicago, IL) (ORA #12121105-IRB01-AM02).

Seven patients had received prior cranial radiation therapy and were offered surgery because of the development of new intracranial lesions. The SRS was delivered to the operative bed within 1 month of surgery in most cases. The patient records were reviewed retrospectively and data regarding the following variables were recorded: age, sex, primary pathology, extent of extracranial disease (based on preoperative staging enhanced computed tomography scan (CT) of the chest, abdomen, and pelvis), the number and size of cerebral metastases, extent of resection (gross vs. subtotal as evidenced by 24-hour postoperative magnetic resonance imaging (MRI) scan), post operative complications, duration of corticosteroid use, corticosteroid-related complications, and SRS dose and treatment volume. Additionally, all patients were classified according to the Radiation Oncology Therapy Group (RTOG) Recursive Partioning Analysis (RPA).[9]

The prerequisite for neurosurgical treatment was stable systemic disease and life expectancy greater than 6 months as determined by the patient's oncologist. The choice to proceed with surgical resection was made based upon lesion size, peritumoral edema, and presence of mass effect and/or symptoms. The lesions were all classified by the Sawaya criteria:[43] Grade I lesions are located in noneloquent brain, Grade II lesions in near-eloquent brain, and Grade III lesions in eloquent brain. Eloquent locations in the Sawaya study are the motor/sensory cortices, visual center, speech center, internal capsule, basal ganglia, hypothalamus/thalamus, brainstem, and dentate nucleus.[43]

All patients underwent craniotomy and resection with the assistance of preoperative MRI images for frameless stereotactic guidance. After surgery, a new MRI brain was obtained for SRS planning. Patients were generally mobilized on postoperative day #1 and were seen as outpatients by neurosurgery between 2 and 4 weeks after surgery. SRS typically was given within one month of surgery. Post-SRS patients were seen initially at 6 weeks and then every 3 months with repeat MRI studies at each visit. Additional or expedited neuroimaging was obtained if central nervous system-related signs or symptoms developed. The patient's oncologist provided all systemic cancer care.

On the day of SRS, a stereotactic head frame was placed under local anesthesia and a simulation CT of the head obtained and fused with the MRI scan. The edges of the operative bed were delineated by the neurosurgeon and radiation oncologist on the MR images. Treatment plans for patients treated before March 2012 were designed using a conformal arc technique on a Varian

Trilogy linear accelerator with a Brainlab treatment planning system (Westchester, IL). After March 2012 treatments were conducted on a Varian TruBeam STx (Palo Alto, CA) system with the Brainlab treatment planning system (Westchester, IL) and a frameless technique. All surgical cavities were treated with 1500 to 1600 cGy, and dose selection was based upon the RTOG 90-05 volume dependent SRS guidelines.[44]

Follow-up MRI scans were obtained 1 month after treatment and at 2 to 3 month intervals thereafter. If up to four new lesions were identified on follow-up imaging, they were treated with SRS using the RTOG 90-05 dose/volume scheme[44] if they were larger than 2 cm. For lesions smaller than 2 cm, a dose of 2100 cGy was used. If more than four new lesions were identified, we recommended proceeding with WBRT.

A corticosteroid tapering protocol was utilized that enables patients to be discontinued from this therapy in a timely fashion. The MRI scans of all patients are evaluated for the degree of cerebral edema surrounding a given metastasis, and this is one of the variables considered when deciding to proceed with surgical resection. Patients are started on dexamethasone 4 mg every 6 hours until the first postoperative day. At that time the dose is reduced to dexamethasone 4 mg every 12 hours and then dexamethasone 2 mg every 12 hours the next day. On postoperative day 3 the dose is reduced to 2 mg daily until SRS is completed. After SRS all patients are sent home with a methylprednisolone dose pack that contains 21 tablets of 4 mg each; the dosing regimen can be found in Table 1. The goal is to discontinue corticosteroid therapy after the completion of the methylprednisolone dose pack.

Complications were surgical if they occurred within 30 days or, if later than 30 days, were a direct result of surgical intervention. Complications were transient if they resolved within 30 days of surgery or definitive management, or prolonged if they persisted until last follow-up or death. The criteria proposed by Sawaya *et al*. for classifying complications is applied.[43]

Overall survival and local control were determined by the method of Kaplan and Meier.[21] Statistical significance was considered as $P < 0.05$. The log-rank test was used as the test statistic for comparing median overall survival across groups. Kaplan-Meier Curves, median survival, confidence intervals, and Cox-proportional hazard-ratios were calculated using STATA v9.2 (College Station, TX).

RESULTS

Fifty-nine consecutive patients were treated in the above manner. We present the overall survival (OS), local control (LC), and treatment-related complications for this group of patients.

The tumors originated from different primary cancers [Table 2]. In 27 out of the 59 patients (46%) multiple metastases were identified while the remaining 32 patients (54%) had only a solitary lesion. There were 29 men and 30 women with a mean age of 61 years. Tumor histology is as follows: 3 breast carcinoma, 1 cervical carcinoma, 1 colon adenocarcinoma, 3 head/neck squamous cell carcinoma, 9 melanoma, 38 nonsmall cell lung carcinoma (NSCLC), 1 renal cell carcinoma, 2 sarcoma, and 1 small cell lung carcinoma. The average tumor diameter was 2.5 cm with the largest being 5.8 cm and the smallest 0.8 cm. Fifteen patients (25%) were classified as RPA Class 1, 37 (63%) as RPA Class 2, and

Table 1: Dosing schedule for the methylprednisolone dose pack

Dosing regimen for methylprednisolone dose pack
Day 1: Two tablets before breakfast, one after lunch, one after dinner, and two at bedtime
Day 2: One tablet before breakfast, one after lunch, one after dinner, and two at bedtime
Day 3: One tablet before breakfast, one after lunch, one after dinner, and one at bedtime
Day 4: One tablet before breakfast, one after lunch, and one at bedtime
Day 5: One tablet before breakfast and one at bedtime
Day 6: One tablet before breakfast

Table 2: Patient characteristics

Characteristic	Number
Sex (%)	
M	29
F	30
Age at treatment	61.2 years (range 29-88)
Primary tumor type	
NSCLC	38
Melanoma	9
Small cell lung cancer	1
Head/neck squamous cell carcinoma	3
Sarcoma	2
Renal cell carcinoma	1
Breast carcinoma	3
Cervical cancer	1
Colon adenocarcinoma	1
Mean corticosteroid use (weeks)	3.4
RPA Class	
1	15
2	37
3	7
Sawaya grade	
I	25
II	17
III	17

M: Male, F: Female, NSCLC: Non-small cell lung carcinoma, RPA: Recursive partitioning analysis

7 (12%) as RPA Class 3. Thirty-three of 59 patients (56%) had distant metastases at the time of initial resection.

Operative complications are presented in Table 3. There was one case of an acute subdural hematoma that developed in the immediate postoperative period and required emergent evacuation after resection of a melanoma metastasis. One patient suffered new-onset diplopia after surgery, one patient had a worsened hemiparesis, and there was one case of a wound infection. Additionally, one patient developed a deep venous thrombosis (DVT) and pulmonary embolism (PE) in the 30-day postoperative period that required treatment. The overall neurological/regional complication rate was 6.8%. The systemic complication rate was 1.7%. There were two complications associated with SRS therapy in this series (2.4%).

Patients underwent SRS treatment at a mean of 3.5 weeks (1-224 days) after surgery. The postoperative bed was treated with a mean dose of 1600 cGy (range 1500 cGy in a single fraction to 3000 cGy given in 5 fractions) to the 90% isodose line. The mean target volume was 13.1 cm^3. Three thousand centigray in 5 fractions were used when the target volume was equivalent to a sphere larger than 3 cm in diameter.

Mean follow-up was 14.4 months (median 12.0 months, range 0.9-62.9 months). The median OS was 15.25 months (95% CI: 11.74-24.20 months) [Figure 1]. Overall survival was 15.95 months in RPA class 1, 15.48 months in RPA class 2, and 8.38 months in RPA class 3 [Figure 2]. The Cox-proportional hazards ratio (HR) was 2.54 (95% CI 1.03-6.26) for RPA Class 3. There was no difference in median overall survival between RPA class 1 and 2 ($P = 0.6107$). A single patient experienced local recurrence of disease subsequent to SRS, which occurred at 44 days post-SRS, and 5.9 months post resection; this recurrence was treated with a second SRS procedure.

Table 3: Surgical and systemic complications

Patient	Complication	Treatment
1	Acute SDH	Surgical evacuation
2	Diplopia	Observation
3	Worsened hemiparesis	Observation/corticosteroids
4	Wound infection	Revision
5	DVT/PE	Anticoagulation

DVT: Deep venous thrombosis, PE: Pulmonary embolism, SDH: Subdural hematoma

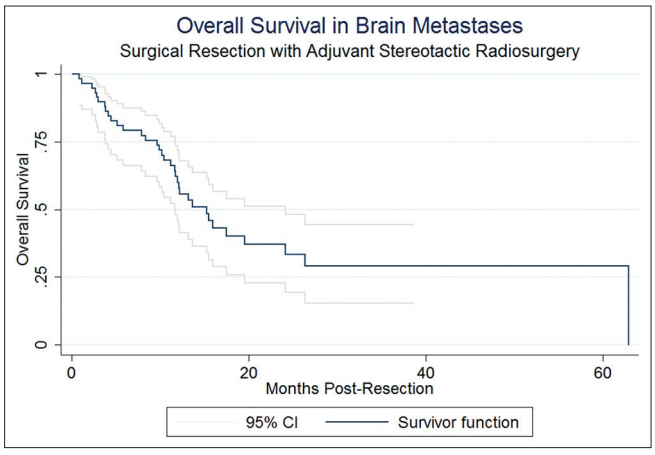

Figure 1: Kaplan–Meier curve of overall survival

Corticosteroid protocol

Corticosteroids in the form of dexamethasone were given to all patients in the immediate preoperative period and then rapidly tapered postoperatively. Thereafter, the radiation oncologist managed the corticosteroid regimen. A standard methylprednisolone dose pack (6 days of therapy) was given to all patients after SRS treatment. All patients received gastrointestinal (GI) prophylaxis in the form of a proton pump inhibitor or H2-blocker. The mean duration of corticosteroid use from the time of diagnosis before surgery to after completion of SRS treatment was 3.4 weeks. At 1 month, 12 patients (20.3%) remained on corticosteroids, at 3 months 4 patients (6.8%), at 6 months 1 patient (1.7%), and at 12 months no patients remained on corticosteroid therapy. The reasons patients were maintained on corticosteroids past the end point of our protocol was due to peritumoral edema seen on MRI scan (8 patients), worsening neurological deficit upon wean (3 patients), and leptomeningeal disease (1 patient).

Complications related to corticosteroid therapy were seen in 91.5% of patients (54/59) and most commonly occurred in the form of hyperglycemia (34/59 patients, 57.6%). Peripheral edema and depression occurred in six patients each (10.2%). There were four (6.8%) DVT and one case (1.7%) of a PE. One patient (1.7%) experienced delayed wound healing, one patient had pneumonia, and there was one GI bleed. There were no cases of oropharyngeal candidiasis, gastritis, Cushing's syndrome,

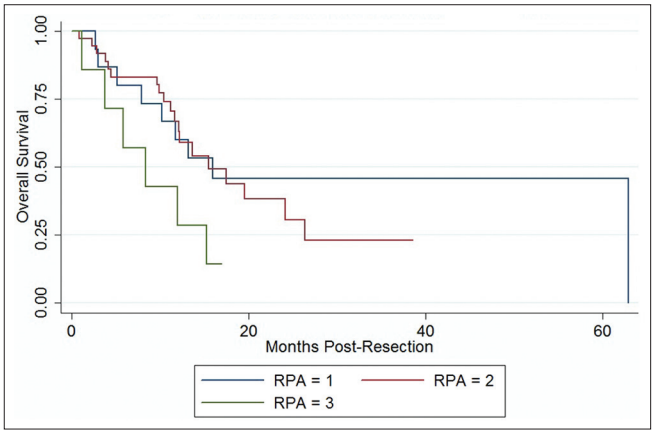

Figure 2: Kaplan–Meier curve of survival by RPA Class. RPA = recursive partitioning analysis

steroid psychosis, or steroid myopathy. A full listing of corticosteroid-related complications is found in Table 4.

DISCUSSION

The use of adjuvant WBRT following resection in patients with cerebral metastases has been the standard of care,[36] but recently treatment with SRS to the resection cavity has been explored.[17,22,31,38] The rationale for adjuvant SRS in lieu of WBRT is to maintain the local control benefits of radiation and surgery while avoiding the now-recognized deleterious cognitive effects of WBRT[5] and maintaining comparable overall survival with this approach.[1]

The local control rate at 1 year observed in this study, 98.3% (1 recurrence), compares favorably to the published literature. Karlovits *et al.* reported a local control of 92.3% while Robbins *et al.*, reported 81.2%.[22,38] Both the studies were conducted retrospectively and contained patients who had undergone surgical resection followed by SRS. Hartford *et al.* reported on a similar group with a local control rate of 85.5%.[11]

Overall survival in this series was 15.25 months and compares well to the literature. Most contemporary series report an OS of 10-20 months.[6,14,16,17,22,31,46] This also compares well with the combined results from prior randomized-controlled trials of various alternate treatment regimens: Surgical Resection + WBRT (median OS 9.07 months), SRS + WBRT (median OS 8.07 months), and WBRT alone (median OS 5.95 months).[10,19,20,24] In our data set we found significantly greater OS in patients who were RPA Class 1 or 2. In this group (n = 52) median OS was 15.94 months, while median OS in RPA Class 3 patients was 8.38 months (P = 0.0358).

Salvage WBRT was required in 42.4% of patient in this study and in all cases was due to the detection of new distant metastases. There was no statistically significant factor associated with this but it can be attributed to the inevitable progression of the disease course.

Table 4: Corticosteroid side effects

Side Effect	Number	%
Hyperglycemia	34	57.6
Peripheral edema	6	10.2
Depression	6	10.2
Deep venous thrombosis	4	6.8
Pulmonary embolism	1	1.7
Delayed wound healing	1	1.7
GI bleed	1	1.7
Gastritis	0	0
Pneumonia	1	1.7
Cushing's syndrome	0	0
Oropharyngeal candidiasis	0	0
Steroid myopathy	0	0

GI: Gastrointestinal

Corticosteroids remain a mainstay of therapy for cerebral metastases and their effectiveness at reducing symptoms from cerebral edema in this patient population is well documented.[8,12,13,15,27,40,41,47,49] Our group considers the discontinuation of corticosteroid therapy as a primary goal of care in addition to prolonging OS and minimizing complications. Patients seen by our group who have evidence of significant cerebral edema on MRI scan will be more likely to receive surgical resection of their metastasis because we feel that the risk of corticosteroid dependence will be reduced with this approach.

The corticosteroid tapering protocol implemented by our group has proven to be very effective at weaning patients from this therapy. There are very few other reports in the literature that address this topic[48] although there are abundant recommendations to taper corticosteroids as quickly as possible.[12,18,40,41,45,47] Corticosteroids are often continued for long periods in patients who harbor lesions in eloquent brain;[25] our experience with surgical treatment of these lesions has been previously published.[30]

Side effects of corticosteroid therapy and their impact on the patient are important considerations as they are frequent and confer morbidity.[12,40,52] They include hyperglycemia, DVT/PE formation, poor wound healing, gastritis and GI bleeds, iatrogenic Cushing's syndrome, and steroid myopathy. Another important, but often not considered, side effect is steroid psychosis.[39] Steroid myopathy is often overlooked in cancer patients who are receiving corticosteroids because the symptoms can be misidentified as secondary to progression of disease; however, this entity is relatively common, severely debilitating, and may be reversible with discontinuation of the agent.[2]

The overall prevalence of side effects in this study is high (91.5% of patients). This is expected in a patient population treated with high-dose dexamethasone. The incidence of specific side effects such as hyperglycemia, DVT, and PE are in line with what literature has been published on the topic.[12] Notably, there are no cases of Cushing's syndrome, steroid psychosis, or steroid myopathy in this series; these complications carry a high morbidity for the patient. It is also important to note that the incidence of steroid dependence is very low: 20.3% at 1 month, 6.8% at 3 months, 1.7% at 6 months, and 0% at 12 months. To our knowledge, no other series of patients receiving SRS after resection with such data has been published. Williams *et al.* reported that, in their large series of patients who received only SRS, corticosteroid dependency was associated with 32% of cases overall and was present in 8% of patient

at 12 months.[53] Our results demonstrate that tailoring therapy to maximize the likelihood of corticosteroid discontinuation reduces dependence and, thus, long-term and serious complications associated with this therapy.

Surgical complications

The complication rate as related to surgery was 6.8% in this series and compares well to that reported by Sawaya *et al.*[43] There is little reported in the literature on surgical complication rates in these patients. Jensen *et al.*reported only two cases out of a series of 106 patients that experiences a complication; one was the development of hydrocephalus postoperatively and the other was a CSF fistula.[17] Vecht *et al.* described one intracranial hematoma and three postoperative wound infections in a series of 63 patients.[51] Mintz *et al.* report three postoperative hematomas and one wound infection identified via a Cochrane review.[29]

Two of the complications in this series required further surgery. All complications are presented in Table 3. Patient 1 in Table 2 required immediate evacuation of an acute SDH after resection of a melanoma metastasis. The complication was promptly diagnosed when he exhibited worsened mental status and a hemiparesis upon emergence from anesthesia. He suffered no permanent neurological sequelae. Patient 2 in Table 2 had undergone resection of a cerebellar metastasis and presented 6 weeks after surgery with dehiscence of the suboccipital incision. Intraoperative cultures grew methicillin resistant *Staphylococcus aureus* (MRSA). He underwent revision of the wound and completed a course of vancomycin. Patient 5 in Table 2 was diagnosed with a DVT/PE 2 weeks after surgery and was cleared to undergo anticoagulation therapy. These results show that surgical complications for this patient population can be held in line with the published literature on the topic.

SRS complications

There were two complications associated with SRS therapy in this series (2.4%). One patient developed a MRSA infection in the head frame pin site and underwent a course of antibiotics. Another patient who harbored a pontine metastasis that was not resected and was treated concurrently with the resection cavity experienced exacerbation of a preexisting hemiparesis. This complication rate is lower than other published reports that utilized SRS without surgical resection.[7,53] This may be due to the lower dose of radiation needed to treat the resection cavity alone versus treating an unresected lesion. Radiation doses required for treatment of unresected lesions can be more than 2000 cGy[23,53] while doses needed for salvage therapy are even higher.[50,56] Other studies such as that by Williams *et al.*, reported a complication rate of 40% while Yamamoto *et al.* reported a long-term complication rate after SRS alone of 10.2%.[53,54] Studies examining short-term results of SRS therapy without surgery have reported complication rates of 2%.[55] Our results support our belief that resecting metastases prior to delivering SRS reduces the complication rate of this therapy.

Cerebral metastases can be treated with a variety of modalities. While the standard of care for resected lesions remains postoperative WBRT, SRS to the resection cavity has been shown to be effective with a better side effect profile. Corticosteroid therapy is a cornerstone of treatment for symptomatic metastases but has significant side effects. The corticosteroid tapering protocol used at our institution has been effective at reducing corticosteroid dependency in this patient population.

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