Surgical Neurology International

SNI: Neuro-Oncology, a supplement to Surgical Neurology International

OPEN ACCESS

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Editor: Daniel Silbergeld, University of Washington Medical Center, Seattle, Washington, USA

Stereotactic radiosurgery for brain metastases from malignant melanoma

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Received: 22 November 14 Accepted: 22 April 15 Published: 20 August 15

This article may be cited as:
Christ SM, Mahadevan A, Floyd SR, Lam FC, Chen CC, Wong ET, *et al.* Stereotactic radiosurgery for brain metastases from malignant melanoma. Surg Neurol Int 2015;6:S355-65.
http://surgicalneurologyint.com/Stereotactic-radiosurgery-for-brain-metastases-from-malignant-melanoma/

Abstract

Background: Surgical resection and stereotactic radiosurgery (SRS) are well-established treatment methods for patients with brain metastases, yet their respective roles in the management of brain metastases remain incompletely defined.

Methods: To report on the role of SRS in the treatment of patients with brain metastases from malignant melanoma, a retrospective analysis of 381 intracranial melanoma metastases in 103 consecutive patients who underwent SRS between 2005 and 2011 at Beth Israel Deaconess Medical Center was conducted. The Cyberknife® SRS system was used to treat all patients. Clinical, technical, and radiographic data were recorded at presentation and on follow-up.

Results: The patient cohort consisted of 40 female (39%) and 63 male (61%) patients with a median age of 57 years. The median overall survival from the time of radiosurgery for the entire patient cohort was 7.6 months. The local control rate at 1-year was 72% for the patients who received surgery followed by SRS and 55% for the entire patient population. Surgery followed by SRS was associated with significantly improved overall survival compared with SRS alone or whole-brain radiation therapy followed by salvage SRS ($P < 0.0057$).

Conclusions: Both surgery plus SRS and SRS provide comparable local control. Despite the difference in lesion size in the subgroups who received surgery plus SRS and radiosurgery alone, similar outcomes were achieved in both groups, suggesting that surgical treatment of larger lesions can yield results that are not significantly different from small lesions treated by SRS alone.

Key Words: Brain metastasis, CyberKnife, melanoma, stereotactic radiosurgery

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.163315
Quick Response Code:

INTRODUCTION

Cutaneous malignant melanoma (MM) is the fifth most common cancer in males and the sixth most common form of cancer in females.[36] Of all tumor histologies, it has one of the highest propensities to metastasize to the central nervous system (CNS), making it the third most common cause of CNS metastasis after lung and breast carcinoma.[1]

CNS metastases occur in 10–40% of patients with Stage IV MM and have been found in 55–75% of patients with MM at autopsy.[2] MM metastases tend to be multiple rather than single at initial presentation.[35] Historically, MM has been considered a radioresistant tumor.[19] Despite several treatment options, which include whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgery, and systemic therapy, the overall prognosis for overall survival (OS) of these patients remains poor.[11] The success of treatment, as measured in OS, is limited due to both high rates of systemic disease progression and local treatment failure. Symptomatic CNS lesions amendable to surgical intervention are often resected before undergoing WBRT or SRS. WBRT alone has resulted in disappointing outcomes in prospective trials, with median survival ranging from 3 to 4 months.[2,11] Over the last decade, the use of SRS as a primary treatment modality has increased and can yield excellent local control rates with prolonged survival and minimal toxicity in selected patients.[16,35] Despite this, its role in the management of brain metastases (BM) from MM, particularly in the setting of surgical resection and WBRT, remains incompletely understood. To this end, we have reviewed a cohort of patients with MM who underwent SRS for CNS disease at Beth Israel Deaconess Medical Center (BIDMC) between 2005 and 2011. The data set of this series of patients was analyzed for specific variables contributing to OS, local tumor control rates (LCR), and progression-free survival (PFS) from distal CNS disease.

MATERIALS AND METHODS

Study design and data collection

In planning and designing this study, similar series served as inspirational source and we closely looked at the studies of Bernard *et al*., Liew *et al*., Hara *et al*., Gaudy-Marqueste *et al*., Selek *et al*., and others.[3,13,16,25,35] When compiling the data for this study, clinical, technical, and outcomes data entries were retrospectively reviewed and recorded. Patient characteristics and clinical data were obtained in a review of the patients' complete medical records. Physics and technical data for each patient were extracted from a longitudinal database of the BIDMC CyberKnife (CK) Center stored by standard CK Multiplan Software (Version 8.5, Accuray, Sunnyvale, CA). Imaging studies were reviewed for each individual case pretreatment, for treatment and at the respective follow-up intervals, and formal radiological notes were incorporated in the assessment of radiographic tumor response. Like in the paper of Liew *et al*., in cases where no autopsy information was found, the presumed cause of death (neurological vs. nonneurological) was judged by evaluation of medical records, the clinical status of the patients' disease and last imaging results.[25] Available information was matched to other entries in the cancer center tumor registry at BIDMC. Data were collected by personnel not directly involved in patient care or any treatment decision-making process. The study design and analysis were approved by the Institutional Review Board (IRB) of Dana-Farber/Harvard Cancer Center (DF/HCC) (IRB# 09-451).

Patient population

The study cohort is comprised of a total of 381 distinct lesions from 103 patients who were treated with CK SRS (Accuray, Sunnyvale, CA) by the Departments of Radiation Oncology and Neurosurgery at BIDMC between January 2005 and December 2011. Of those, 41 patients (40%) received SRS alone, 21 patients (19%) were treated with SRS as salvage therapy after WBRT and 21 (19%) patients underwent postoperative adjuvant SRS treatment to the resection cavity after conventional image-guided open surgical resection. Prior to treatment with SRS, all patients in the cohort underwent a complete primary as well as systemic work-up. In 94% of the cases, cerebral MM metastasis was diagnosed by magnetic resonance imaging (MRI). For six patients (6%), computed tomography (CT) with and without i.v. contrast was used, as MRI imaging was contraindicated, for example, in cases of contrast allergy (3) or in the setting of cardiac pacemaker placement (3).

Eligibility and inclusion criteria

Patients who underwent SRS met the following widely-used eligibility criteria: (a) All patients were adults; (b) all patients had histologic confirmation of MM either at the primary site or at a site of metastatic disease; (c) greatest tumor diameter was limited to tumors measuring less than 3 cm prior to resection; and (d) no major, sustained neurologic deficit due to mass effect was present during treatment time. In patients where large tumor masses were causing significant neurologic symptoms (which did not improve after corticosteroid application) a craniotomy was undertaken whenever the tumor was accessible and located in a noneloquent region of the brain.

Follow-up

First posttreatment MRI and clinical follow-up examination were routinely obtained at 1 month after SRS. Subsequent MRI scans and clinical follow-up examinations were obtained every 2–3 months. Follow-up assessment was scheduled for surveillance at set intervals even in patients who remained clinically asymptomatic. A lesion was classified as local failure in all patients where at least one of the following conditions was met: (a) An increase in lesion size in gadolinium enhanced MRI, and (b) SRS-related complications such as symptomatic hemorrhage or (c) features unclear of radiation necrosis in follow-up imaging requiring surgical intervention. Cerebral metastasis in a location other than the previous tumor locations was categorized as distant failure. Eight patients (8%) transferred care to other facilities and no radiographic follow-up data was available. These patients were excluded from the tumor control analysis. For the

remaining 95 of the 103 original study patients, the clinical development was continuously recorded. Patients and lesions were included into the analysis after at least a year had passed since the final patient received radiosurgery treatment. Fairly similar criteria were used in the study by Selek *et al*.[35]

Statistical methods

Descriptive statistics as well as frequencies were obtained for multiple variables. The Fisher's exact test and the Kruskal–Wallis test were used to examine the homogeneity of patient groups. The distribution of the different treatment modalities was approximately uniform over the examined time span. Kaplan–Meier analyses were therefore performed to calculate OS, LTC, and PFS. Posttreatment time intervals were assessed in months and are based on the start date of SRS treatment and the last imaging date or the last follow-up date. For categorical variables, univariate analysis in form of the log-rank was employed. Cox proportional hazards model was used for univariate analysis of continuous variables and in the assessment of the prognostic value of different variables in multivariate analysis. Due to the unfavorable observations to variables ratio, we opted for stepwise regression by forward selection in multivariate Cox analysis with stringent criteria to avoid overfitting the data. Statistical significance was defined as a *P* value of less than 0.05 in both univariate and multivariate analyses. All statistical calculations were performed using the STATA 11.0 software package (STATA Corp., College Station, TX, USA).

RESULTS

Patient demographics

The entire patient cohort consisted of 40 female (39%) and 63 male (61%) patients, aged between 28 and 92 years (mean age 57 years, median age 57 years) at the time of their initial BM diagnosis. When the patients first presented, their Karnofsky performance status (KPS) was 90 (range, 40-100). Fifty-two patients (50.5%) presented with a single metastasis, 51 patients (49.5%) had multiple metastases at initial presentation. Twenty-one patients (20%) had four or more metastases. Three hundred and fifty (92%) lesions of this data set were located supratentorially. When SRS treatment was initially undertaken, a systemic survey was conducted in all patients, which included both a CT torso and in some cases a positron emission tomography (PET)-CT. The status of the extra-cranial melanoma was classified as controlled in 66 patients (64%). The primary skin lesions were located on the trunk in 31 patients (31%); in 29 patients (28%) the initial skin lesion was found on the extremities; 23 patients (22%) presented with lesions in the head and neck region; 2 patients (2%) had ocular melanoma, 2 patients (2%) had vaginal melanoma; and in 16 patients (15%) the primary tumor location remained unknown. At the time of initial SRS treatment, 15 patients (15%) were found to have either no evidence of systemic disease (NED) or were in complete clinical remission (CR). As Selek *et al*., we also classified our patients along the lines of the following commonly used prognostic indices.[35] According to the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA), 86 patients (83%) were classified as RPA class II, 10 (10%) were RPA class III, and 7 (7%) were RPA class I. To make the data set more easily comparable to existing literature, we also employed other well established classification systems: The Score Index for Radiosurgery (SIR) is another tool of prognostic determination for patients with BM submitted to radiosurgery and was developed by Weltman *et al*.[39] It comprises age, KPS, systemic disease, largest lesion volume, and the number of lesions, and was shown to have a better prognostic accuracy than RPA partitioning in a small patient cohort of 65 patients. The SIR was used to stratify our patient cohort into 71 patients (69%) with a score less than or equal to 6, and 32 patients (31%) with a score greater than 6. The Disease-specific Graded Prognostic Assessment (Ds-GPA) is a diagnosis-specific prognostic tool that takes into account the fact that the prognosis of patients with BM varies by primary tumor histology. Introduced by Sperduto *et al*., it established KPS and the number of BMs to be the most robust factors to predict survival outcome in their 481 analyzed patients with BMs from MM.[37] According to the Ds-GPA, 35 patients (34%) were classified as Ds-GPA 4, 28 (27%) as Ds-GPA 3, 32 (31%) as Ds-GPA 2, 7 (7%) Ds-GPA 1, and 1 (1%) Ds-GPA 0. The compositions of these three

Table 1: Composition of the RPA prognostic index

RPA class*	Clinical parameters	Median OS (months)
I	<65 years; KPS≥70; controlled primary; no extracranial spread	7.1
II	≥65 years; KPS≥70; controlled primary; extracranial spread	4.2
III	KPS<70	2.3

RPA: Recursive partitioning analysis, KPS: Karnofsky performance status, KPS: Karnofsky performance status, OS: Overall survival. *The RPA classification is based on the system of Gaspar *et al*.[12]

Table 2: Composition of the SIR prognostic index

Parameter	SIR score*		
	0	1	2
Age (years)	≥60	51-59	≤50
KPS	≤50	50-70	>70
Systemic disease	PD	PR/SD	CR/NED
Largest lesion volume (cm^3)	>13	5-13	<5
Number of lesions	>3	2	1

SIR: Score index of radiosurgery, KPS: Karnofsky performance status, PD: Progressive disease, PR: Partial remission, SD: Stable disease, CR: Complete remission, NED: No evidence of disease. *The SIR index is based on the classification system of Weltman *et al*.[39]

Table 3: Composition of the Ds-GPA prognostic index for melanoma

Parameter	Melanoma-GPA scoring criteria*		
	0	1.0	2.0
KPS	<70	70-80	90-100
Number of BM	>3	2-3	1

Ds-GPA: Disease-specific graded prognostic assessment, KPS: Karnofsky performance status, BM: Brain metastasis, Median overall survival (months) by GPA: 0-1.0=3.4; 1.5-2.0=4.7; 2.5-3.0=8.8; 3.5-4.0=13.2. *The Ds-GPA originally stems from the RPA classification and was refined by Sperduto *et al.*[37]

Table 4: Patient characteristics

Characteristics	*n* (%)
# of patients	103
# of lesions	381
Age	
Median age (years)	57
Mean age (years)	57
Range (years)	28-92
Sex	
Male	63 (61)
Female	40 (39)
Karnofsky performance status	
>70	74 (72)
≤70	29 (28)
# of brain metastases	
1	53 (51)
2	18 (17)
3	11 (11)
>3	21 (21)
Primary status at SRS	
Controlled	66 (64)
Uncontrolled	37 (36)
Systemic disease status at SRS	
No evidence of disease	11 (10)
Complete remission	4 (4)
Partial remission	3 (3)
Stable disease	9 (9)
Progressive disease	76 (74)
Recursive partitioning analysis*	
Class 1	7 (7)
Class 2	86 (83)
Class 3	10 (10)
Score index for radiosurgery*	
>6	32 (31)
≤6	71 (69)
Melanoma graded prognostic assessment*	
Group 0	1 (1)
Group 1	7 (7)
Group 2	32 (31)
Group 3	28 (27)
Group 4	35 (34)

SRS: Stereotactic radiosurgery. *Patients were categorized on the basis of the respective criteria in Tables 1-3

prognostic indices are summarized in Tables 1-3. Patient characteristics of all 103 patients are displayed in Table 4.

Treatment characteristics

CK SRS was employed separately from any ongoing systemic treatment regimen for extracranial metastatic disease. In patients fulfilling the outlined eligibility and inclusion criteria for SRS treatment, all newly diagnosed and visible brain lesions were treated. A total of 183 SRS sessions were performed on 381 lesions in multiple plans. An average of two lesions was irradiated during each session (range, 1–7). The median individual tumor target volume was 0.68 cm^3 (mean, 2.97 cm^3; range, 0.04–81.04 cm^3), the median prescription dose was 22 Gy (mean, 20 Gy; range, 5–22 Gy), and the median conformality index was 1.28 (mean, 1.43; range, 1.00–10.02). The median prescribed isodose line was 77% (range, 61–95%). Twenty-one patients (20%) underwent surgical resection before SRS treatment, and 21 patients (20%) had received prior WBRT (median, 30; range, 20–51 Gy). All patients received prophylactic corticosteroids (dexamethasone) and antiseizure medication (levetiracetam) during and after SRS treatment. Additional therapies included standard systemic therapy (IL-2, Ipilimumab, Dacarbacine, and Vemurafenib) in 14 patients (14%), IRB-approved experimental study therapy regimens (e.g., CTLA-AB, RAF265, ILX561, or PD-1-AB) in 37 patients (36%), or a combination of both in 52 patients (50%). Seventy-seven patients (75%) had received systemic therapy prior to SRS treatment, 20 patients (19%) had systemic treatment concurrent with or after SRS, and 6 (6%) had not yet received systemic therapy at all when the SRS treatment was undertaken. A summary of treatment parameters is presented in Table 5.

Overall patient survival

At the time of analysis (12 months after the last patient underwent SRS treatment), 86 patients (84%) were dead and 17 patients (16%) were alive. According to the data obtained in this study, 24 patients (23%) deceased from progression of brain disease (neurological death), 45 patients (44%) succumbed to systemic disease progression (nonneurological death), and in 34 patients (33%) the cause of death was unknown. The median OS after SRS was 7.6 months (95% CI 5.1–10.3 months) for the entire study population. The median OS from the diagnosis of the first BM was 11.0 months (95% CI 9.3–13.3 months) and 51.8 months (95% CI 40.8–74.8 months) from the diagnosis of the primary site malignancy. Actuarial survival rates for the entire patient cohort were 95.2% (n = 99) at 1 month, 78.6% (n = 81) at 3 months, 56.0% (n = 56) at 6 months, 34.8% (n = 32) at 12 months, and 20.2% (n = 19) at 24 months. The Kaplan–Meier plot for OS for the entire patient cohort is displayed in Figure 1.

Table 5: Treatment characteristics

Parameters	*n* (%)
Stereotactic radiosurgery	
Median tumor vol. (cm^3)	0.68
Range tumor vol. (cm^3)	0.43-81.04
Median no. of beams	204
Median monitor units	15,358
Median dose (Gy)	22
Median no. fractions	1
Median coverage (%)	97
Median isodose line (%)	77
Median conformality index	1.28
Median heterogeneity index	0
Median min dose (Gy)	20
Median max dose (Gy)	27
Surgical resection	
N	21 (20)
Gross total resection	20 (95)
Whole-brain radiation therapy	
N	21 (20)
Median dose (Gy)	30
Dose range (Gy)	20-51
Systemic therapy	
N	103 (100)
Standard therapy	14 (14)
Experimental therapy	37 (36)
Both	52 (50)

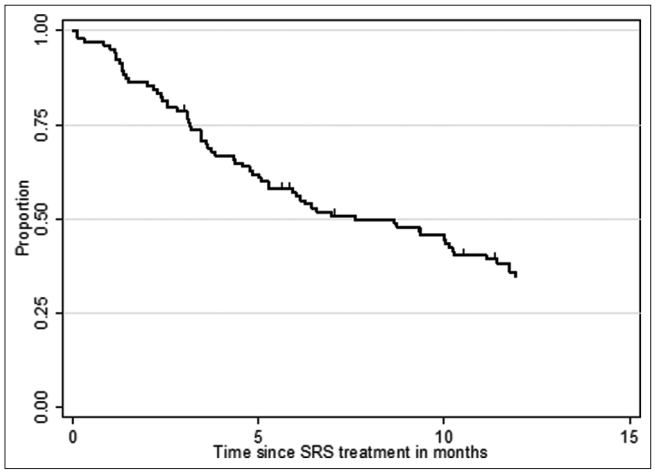

Figure 1: Kaplan–Meier plot showing overall survival for the entire study population

The median OS after SRS for the 52 patients with a single metastasis was 11.7 months (95% CI 8.67–15.76) compared with only 5.1 months (95% CI 3.10–6.43) for the 51 patients with multiple ($n > 3$) CNS metastases ($P = 0.0017$). Median OS was significantly different for the three RPA classes ($P = 0.0092$). Whereas RPA class I patients had a median OS of 33.6 months, RPA class II and III patients had a median OS of 7.6 and 3.2 months, respectively [Figure 2].

When stratifying the patient cohort by treatment modality, patients who were previously treated with WBRT followed by salvage SRS for recurrences (21 patients) did particularly poorly with a median OS after SRS of 3.43 months (95% CI 2.37–5.26). In contrast, patients who received SRS alone (41 patients) and surgical resection followed by SRS (21 patients) had a median OS of 6.57 months (95% CI 3.43–11.13) and 12.53 months (95% CI 6.43–33.57), respectively [Figure 3].

The actuarial 1-year OS rates were 29.6% for SRS alone, 54.1% for surgery plus SRS, and 15.4% for WBRT plus SRS ($P = 0.0058$). In univariate analysis, we found that KPS (≥70 vs. <70; $P = 0.0092$), the number of cerebral metastases (<3 vs. ≥3 lesions; $P = 0.01$), systemic disease status (PR/CR/NED vs. PD/SD; $P = 0.0069$), and surgical resection ($P = 0.0432$) were factors significantly associated with better OS. Prior WBRT ($P = 0.0162$) was found to be significantly associated with poor OS. The following prognostic factors were not found to be significantly associated with a survival difference in our patient cohort: Sex, age, primary status, and tumor volume. Moreover, in univariate analysis, the three prognostic indices RPA ($P = 0.0092$), Ds-GPA ($P = 0.0012$), and SIR (≥6 vs. <6; $P = 0.0001$) were prognostic in our patient cohort. In multivariate Cox analysis, factors associated with a significantly better OS were the number of cerebral metastases ($P = 0.009$), the status of systemic disease ($P = 0.008$), the RPA class ($P = 0.006$) and the Ds-GPA group ($P = 0.031$). The SIR score was not found to be significant in multivariate analysis. In subgroup analysis, when comparing the survival outcomes of the two patient groups who received SRS alone or surgery plus SRS, we found that the groups were fairly homogenous in terms of patient characteristics [Table 6]. Multivariate analysis in these two subgroups yielded significant results for KPS (≥70 vs. <70; $P = 0.040$), the number of cerebral metastases (<3 vs. ≥3 lesions; $P = 0.044$) and the treatment modality (surgery plus SRS vs. SRS alone; $P = 0.008$). The regression results are displayed in Table 7.

Analysis of patients with a single brain lesion and systemic disease control was limited by the small number of patients in these subgroups. While 22, 15, and 4 patients in the SRS, surgery plus SRS, and WBRT groups had a single brain lesion, only 4, 6, and 2 patients, respectively, had controlled systemic disease. Nevertheless, number of brain metastasis as a categorical (1 vs. multiple) or continuous variable was significant for OS in multivariable analysis independent of systemic disease status.

Local tumor control

Follow-up imaging studies were available for 356 tumor lesions in 95 patients (92%). The mean patient follow-up was 10.7 months. Over the course of the entire follow-up

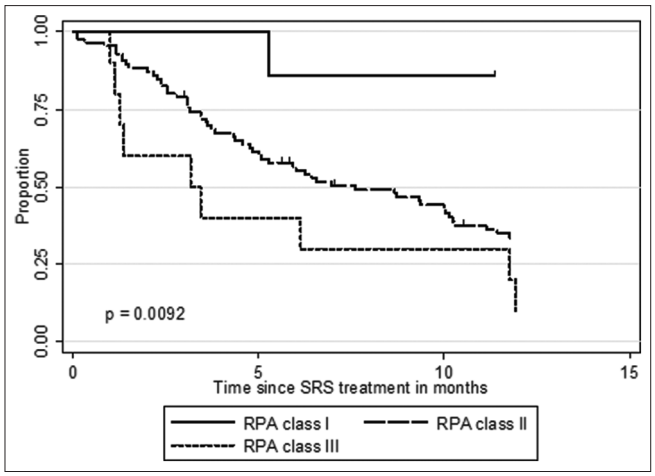

Figure 2: Kaplan–Meier plot showing overall survival for the three RPA classes

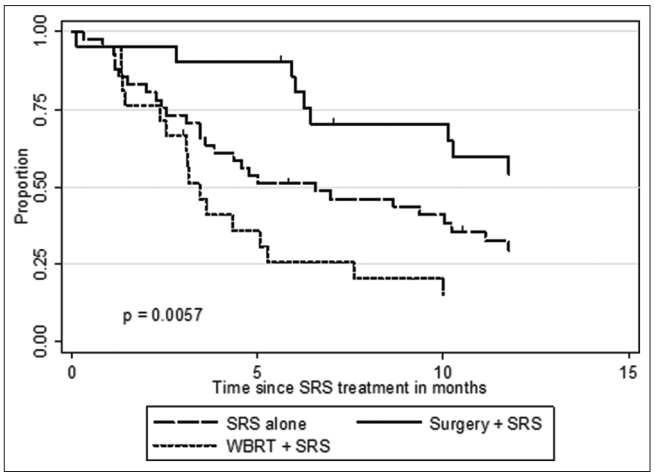

Figure 3: Kaplan–Meier plot showing overall survival for the three different treatment groups

Table 6: Patient characteristics of the SRS and surgery plus SRS treatment groups

	SRS	Surgery + SRS	*P*
# of patients	41	21	
Age			
Median age (years)	53	46	
Mean age (years)	55	50	
Range (years)	(25-88)	(26-77)	
Sex			
Male	29 (71%)	15 (71%)	1.0000
Female	12 (29%)	6 (29%)	
Karnofsky perf. status			
>70	30 (73%)	17 (81%)	0.5505
≤70	11 (27%)	4 (19%)	
#BM			
<3	30 (73%)	18 (85%)	0.3458
≥3	11 (27%)	3 (15%)	
Primary status at SRS			
Controlled	24 (59%)	14 (67%)	0.5915
Uncontrolled	17 (41%)	7 (33%)	
Systemic disease status at SRS			
NED/CR/PR	4 (10%)	6 (29%)	0.0747
SD/PD	37 (90%)	15 (71%)	
RPA			
Class II	39 (95%)	17 (80%)	0.1674
Class I/III	2 (5%)	4 (20%)	
SIR			
>6	13 (32%)	11 (52%)	0.1684
≤6	28 (68%)	10 (48%)	
Ds-GPA			
Group 1/2	11 (26%)	5 (24%)	0.5262
Group 3/4	30 (74%)	16 (76%)	
Median tumor vol. (cm3)	0.901	7.627	0.0001

BM: Brain metastasis, SRS: Stereotactic radiosurgery, NED: No evidence of disease, CR: Complete remission, PR: Partial remission, SD: Stable disease, PD: Progressive disease, RPA: Recursive partioning analysis, SIR: Score index of radiosurgery, Ds-GPA: Disease-specific graded prognostic assessment

period, local control was achieved in 71.1% of treated lesions (253 of 356 lesions). For the entire patient cohort, the 1-year incidence of local tumor control was 54.9%. Of the 41 patients who received SRS alone, local failure was noted in 14 patients (34.1%) in at least one lesion at some point in time, and 6 patients (28.6%) in the surgery group showed evidence of recurrent disease at the treatment site sometime during the follow-up period. In this series, the 1-year LCR was higher for patients who underwent SRS alone (68.5%) or surgery plus SRS (71.8%) compared to patients who received WBRT (16.4%) ($P = 0.0042$). Figure 4 shows the Kaplan–Meier estimates for local tumor control stratified according to treatment modality.

While the most significant variable for LCR in univariate log-rank analysis ($P = 0.000$) and multivariate Cox regression ($P = 0.0053$) was tumor volume, the number of BM did not significantly affect local tumor control in our patient cohort. Of all analyzed variables, tumor volume ($P = 0.0210$) and surgical treatment ($P = 0.0219$) significantly affected local PFS in multivariate analysis.

Distant progression-free survival

New brain lesions were discovered in 58 (56%) of 103 patients over the course of follow-up. After SRS treatment, a median of 6.2 months (95% CI 3.37–9.47) elapsed until distal failure occurred. Median distal PFS for patients who received SRS alone, surgery plus SRS, and WBRT plus SRS were 5.7, 11.4, and 7.7 months, respectively. Actuarial rates, capturing freedom from new brain lesions at other locations was 88% at 1 month, 66% at 3 months, 52% at 6 months, and 31% at 12 months after SRS [Figure 5].

In Cox analysis, new cerebral lesions occurred more likely in patients with a worse extracranial disease status ($P = 0.043$). Outcome characteristics of this series have been summarized in Table 8.

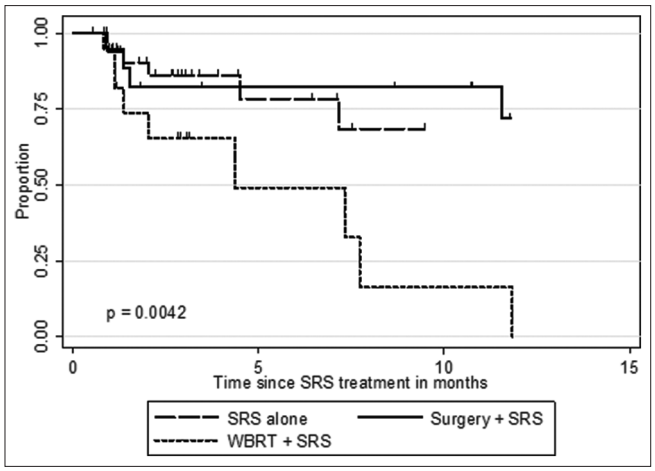

Figure 4: Kaplan–Meier plot showing local control for three different treatment groups

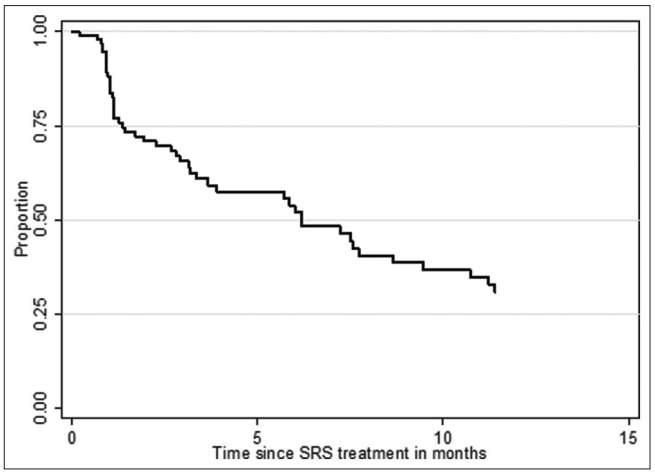

Figure 5: Kaplan–Meier plot showing the proportion of patients without distant failure after radiosurgery

Table 7: Multivariate analysis: Overall survival in SRS and surgery plus SRS subgroups

Variable	Coef.	95% CI	*P*
Sex			
Male vs. female	0.231	–0.484 to 0.945	0.527
Karnofsky			
<70 vs. ≥70	–1.861	–3.638 to 0.085	0.040
# of BM			
<3 vs. ≥3	0.8027	0.020 to 1.585	0.044
Primary status at SRS			
Controlled vs. uncontrolled	–0.554	–1.362 to 0.255	0.180
Systemic disease status at SRS			
NED/CR/PR vs. SD/PD	–0.983	–3.506 to 1.540	0.445
Treatment modality			
Surgery + SRS vs. SRS alone	–3.219	–5.601 to 0.829	0.008

BM: Brain metastasis, SRS: Stereotactic radiosurgery, NED: No evidence of disease, CR: Complete remission, PR: Partial remission, SD: Stable disease, PD: Progressive disease, Coef.: Coefficient, CI: Confidence interval

Table 8: Summary of outcome characteristics of the three treatment groups

	SRS	Surgery + SRS	WBRT + SRS
Median OS (months)	6.5	12.5	3.4
OS (range, in months)	(3.4-11.1)	(6.4-33.6)	(2.4-5.3)
1-year actual OS (%)	30%	54%	15%
2-year actual OS (%)	18%	38%	5%
5-year actual OS (%)	15%	20%	0%
1-month LCR (%)	94%	95%	94%
3-months LCR (%)	86%	82%	65%
6-months LCR (%)	78%	82%	16%
12-months LCR (%)	68%	72%	16%
Median distal PFS (months)	5.7	11.4	7.7
1-year actuarial distal PFS (%)	30%	43%	42%

OS: Overall survival, LCR: Local tumor control rates, PFS: Progression-free survival, SRS: Stereotactic radiosurgery, WBRT: Whole-brain radiation therapy

DISCUSSION

Overall survival and prognostic factors

The primary goal of this study is to report our experience in the treatment of patients with BM from MM treated with SRS, explore the associated role of surgery and prior WBRT and to correlate our findings with previous reports in the literature. Typical therapeutic algorithms for patients with BMs nowadays comprise WBRT, SRS, surgery or a combination of these modalities.[3] For patients with BMs from MM, it has been reported that they die more often from intracranial causes than patients with BMs from other solid organ tumors.[3] The prognosis of metastatic melanoma with CNS-seeding remains grim: Corticosteroids and WBRT do not significantly prolong OS.[14,25,26] Median OS rates have been shown to vary between 5 and 11 months in retrospective studies of patients with BM from MM that have received SRS with or without WBRT.[7,13,16,18,20,24,25,27,35,40] The median OS in our patient cohort with 7.6 months is therefore similar to results reported in the literature [Table 9]. The stark differential in OS of patients who received SRS alone or with surgery plus SRS and those who underwent prior palliative WBRT treatment may partially be attributed to selection bias. In many current treatment algorithms, patients with only one brain lesion are more likely to receive surgical treatment, whereas patients with more advanced disease and several brain lesions are more likely to undergo WBRT or WBRT plus SRS. In 2008, Korn *et al.*, conducted a meta-analysis of 42 Phase II trials which looked at Stage IV MM patients. Median OS in these patients was demonstrated to be 6.2 months (95% CI 5.9–6.5 months).[22] Significant markers for OS in these patients were cerebral and visceral lesions, sex, and overall performance status. In our patient cohort as well, visceral lesions as well as the number of cerebral

Table 9: Overview of selected malignant melanoma brain metastasis studies

Series	Year	No. of patients	No. of lesions	Median tumor volume (cm^3)	Dose range (Gy)	Treatment modality	Median overall survival (months)	12-months local control (%)
Current series	2015	103	381	0.68	20-27	CyberKnife	7.6	68
Bernard *et al.*	2012	54	103	2.10	12-40	CyberKnife	6	68
Liew *et al.*	2011	333	1570	4.10	11-22	GammaKnife	5.6	63
Hara *et al.*	2009	62	145	1.47	14-24	CyberKnife	5	87
Jensen *et al.*	2008	73	280	0.61	15-22	LINAC	7.4	64
Gaudy-Marqueste *et al.*	2006	106	221	1.15	8-22	GammaKnife	5.6	69
Koc *et al.*	2005	26	72	1.72	8-22	GammaKnife	6	n/a
Radbill *et al.*	2004	51	188	0.47	10-21	GammaKnife	6.5	81
Selek *et al.*	2004	103	153	1.9	10-24	LINAC	7.5	60
Mangione *et al.*	2002	45	92	3.63	13-25	GammaKnife	10.4	82
Yu *et al.*	2002	122	332	0.8	14-24	GammaKnife	7	90
Lavine *et al.*	1999	45	93	5.60	16-24	GammaKnife	8	97
Mori *et al.*	1998	60	118	2.95	10-20	LINAC	7	90

SRS: Stereotactic radiosurgery, LINAC: Linear accelerator. This table was adapted from Bernard *et al.*[3]

lesions were significantly correlated with OS. Sex and performance status at the time of treatment, however, did not account for much of the variability in OS, which might be due to the fact that 92 patients (89%) had a KPS of 70 or above at initial presentation.

Surgical resection

The gold standard in patients with one accessible BM, good performance status and limited extracranial disease remains the surgical resection.[28,31,32] In patients with a favorable prognosis yet two or three symptomatic BMs, surgery usually also is a first line strategy.[5,21] The decision of whether or not to undertake surgical excision of a lesion depends on multiple criteria such as lesion size, location as well as personal and institutional preference.[5,21] A large retrospective study by Lagerwaard *et al*. had shown that surgical resection is better than supportive care.[23] A survival advantage for patients undergoing resection has also been shown as improved outcomes when contrasted with OS in patients who received only WBRT.[10] However, both the local tumor recurrence rate and the incidence of neurological complications were significantly reduced where WBRT was added to surgery.[21,33] However, in neither study any improvement in OS was observed. Moreover, there exist repeatedly uttered concerns about cognitive side effects from WBRT treatment.[6,17] Even though surgery has been shown to be superior to WBRT alone, SRS, as a different form of radiation therapy, proved to be a viable and comparable option to surgery in the setting of BMs. To date, no level 1 evidence studies such as prospective randomized studies exist that relate primary SRS and surgical treatment. So far, the data from all available studies of retrospective nature provide indication that clinical outcomes are alike. O'Neill *et al*., for example, found no statistical discrepancy in the OS of 97 patients who had received either surgery or SRS.[30] Lately, the number of various patient cohorts who received SRS instead of surgical treatment increased, probably also due to technical progress. Nonetheless, surgery remains a very important and integral constituent in the multimodal and multidisciplinary handling of patients with singular BM. It is the surgical resection alone that permits the prompt debulking of life-threatening lesions. Surgery also allows for the immediate treatment of symptomatic intracranial hypertension by relieving mass effect and clinically often highly relevant edema, which frequently enables the reestablishment of cerebrospinal fluid (CSF) flow as well as a reduction of steroid medication.[28] In a recent study, Bernard *et al*. reported an improved outcome in a small patient cohort that had surgery to BMs before SRS treatment.[3] Since this is currently the only report of its kind in the literature, its reported observations could be skewed due to the small size of the cohort as well as favorable patient selection, as eligibility for surgical resection likely reflects better systemic condition and can be taken as an indicator for good performance status, younger age, fewer BMs, and a controlled primary, as the authors of this study suggest.[3] Our series confirms the finding of this study, as surgery plus adjunct SRS to the resection cavity was also associated with improved OS in our study. Particular attention should be paid to the difference in the lesion size, while otherwise the subgroups of our patients who received SRS alone or surgery plus SRS were fairly homogenous with respect to patient characteristics. This suggests that surgical resection achieves excellent results even in comparably large lesions resulting in an equally favorable outcome and hence should be kept the first line therapeutic option for patients with resectable BMs from MM in patients in good performance status. These results do not address the burning question whether patients with smaller lesions would benefit from one particular treatment more than from the alternative.

Whole-brain radiation therapy

Traditionally, corticosteroids and WBRT were used to treat BMs.[9,16] Nonrandomized studies have hinted towards WBRT raising median OS time somewhat to approximately 3 to 4 months, from 1 to 2 months without treatment and corticosteroids, respectively.[14,25,26] No WBRT treatment regimen has been shown to be superior to any other and treating BMs from MM and RCC is particularly challenging, as these tumors are known to be especially radioresistant.[9,29,34,38] The role of WBRT in the management of BM from MM therefore remains controversial. According to Eichler *et al*. indications for WBRT primarily center around patients with progressive, active or wide-spread cancer, often with the goal of palliating neurological symptoms.[9] DiLuna *et al*. as well as Selek *et al*. showed no OS benefit for additional WBRT for patients treated with SRS when compared with those receiving SRS alone.[8,35] In our study, patients who received prior WBRT plus SRS did worse in terms of OS and LCR compared with the patient groups who received SRS alone or surgery plus SRS. Whether WBRT would add to improved outcomes when delivered electively, before or after SRS, instead of at recurrence, as reported in our study, can be speculated. A selection bias likely sufficiently explains the finding that these patients do worse (e.g., due to an already existing poor performance status when selected for upfront WBRT). Patients would also have a particularly poor prognosis when treated with WBRT for salvage at the time of recurrence, due to the fact that they already show signs of late stage progressive systemic disease.

Local tumor control

Over the past several years, numerous studies have demonstrated that SRS is an effective treatment option for patients with BM from MM. A comprehensive review of such studies has been provided by Hanson *et al*., which we repeatedly consulted while compiling the following figures.[15] A recent and large study by Liew *et al*. found that GammaKnife (GK) SRS is a successful treatment strategy for patients with BMs from MM, reporting a LCR of 63%.[25] Several smaller studies have also reported LCRs. Clarke *et al*. looked at 27 patients with BM from MM and renal cell carcinoma (RCC) and found that GK SRS is an effective and safe treatment modality for patients with single radioresistant BM, reporting a 1-year LCR of 70%.[7] Hara *et al*., in their analysis of 62 patients with BM from either MM or RCC who received CK SRS, reported a 1-year LCR of as high as 87%.[16] In a series that included only patients with BM from MM, Jensen *et al*. established a 1-year LCR of 64% in 73 patients treated with linear accelerator (LINAC)-based SRS, and Gaudy-Marqueste *et al*. reported a 1-year LCR of 69% in 106 patients treated with GK SRS.[13,18] In another series of 103 patients treated with a LINAC-based system at the University of Texas M. D. Anderson Cancer Center, Selek *et al*. achieved a 1-year LCR of 60% in patients with BM from MM.[35] Older series, like the ones of Yu *et al*., Larvine *et al*., and Mori *et al*. reported higher values for 1-year LCRs, ranging from 82% to 90%.[24,27,40] In our study, the most conservative calculation of the 1-year LCR in all treated patients was found to be 55% according to the Kaplan–Meier method, but was based on a rather wide definition of local failure. In the patient subgroups who were treated with SRS alone or surgery plus SRS 1-year LCRs were 68% and 72%, respectively. Our criteria for local control were very generous as some patients with hemorrhage alone or radiation necrosis may have been included. Nevertheless, our results suggest that surgical resection prior to SRS and SRS alone provide excellent local tumor control. However, the assessment of LCRs remains largely a question of its conceptual and operational definition.[35]

The difficulty of defining and calculating local control rates

Cumulative research shows that LCRs of BM from radioresistant tumor entities like MM and RCC range between 50% and 100%. This huge range is neither entirely explained by varying degrees of expertise at different centers nor by the selection of different patient populations. Instead, it might at least be partially attributable to variations in definitions of local control, differing imaging follow-up schedules, and different methods of calculating LCRs. Just like in the study undertaken by Selek *et al*., we used stringent and conservative criteria with respect to those three aspects.[35] To be precise: To not underreport treatment failure, we used a broad definition of local failure and considered lesions to have locally failed if they (a) had increased in size, and (b) exhibited signs of symptomatic hemorrhage or (c) displayed features of radiation necrosis requiring surgical intervention. Statistical calculations were based on the date of SRS treatment with follow-up entries to the last imaging date. Imaging had routinely been obtained at 1-, 3-, 6-, 12-, and 24-month intervals, as is standard in large cancer centers, if the patient was still alive. As pointed out by Selek *et al*., the accuracy and objectivity of LCRs is highly dependent on imaging interpretation as well as imaging frequency, as otherwise local failure may go unnoticed and such practice would subsequently lead to upward-biased, nonrepresentative tumor control rates.[35] Also, the evaluation of local tumor control is only sensible in such lesions that have imaging films available for at least 3 months after SRS treatment to allow adequate time for local failure detection. Reported LCRs in the literature employ various calculation techniques, including the Kaplan–Meier method as well as proportional reporting at specific imaging dates. In combination with low-frequency imaging schedules, both approaches neglect competing risks such as death from distant brain failure or other

causes, and systematically rule out patients who died close to the next imaging date, thereby artificially upholding or even elevating LCRs. The application of more stringent criteria such as those suggested by Selek *et al.* (documenting any lesional size increase as local failure while systematically obtaining imaging films at prescheduled dates, and calculating LCRs with the Kaplan–Meier method) led to a comparatively low LCR of 55% for our entire patient cohort, which puts the treatment success rate at the low end of the spectrum.[35] However, when selecting subgroups of patients who were treated with SRS alone or surgery plus SRS, we can report LCRs of 68% and 72%, respectively. If we single out patients with KPS ≥ 70, low intracranial tumor burden (<1 brain lesion), and a systemically controlled disease (NED/SD), LCRs in patients who received SRS alone or surgery plus SRS in our patient cohort rose to above 75% and 80%, respectively. Several of these points have been made by Selek *et al.* before, and we agree and strongly suggest that future efforts should therefore be undertaken to standardize LCR reporting and to pay greater attention to patient selection criteria.[35]

A treatment algorithm

Patients with BM from MM are frequently classified into different treatment groups. Gaudy-Marqueste *et al.* have outlined four stylized clinical scenarios which treating clinicians are usually confronted with.[13] In the first scenario, patients present with a solitary brain lesion and no evidence of systemic disease after primary work-up. Both surgical resection and SRS are established approaches in this setting.[4,9] In our study, patients who underwent surgical resection before SRS treatment to the resection cavity (n = 41) had a better OS than patients who received SRS alone, potentially suggesting that surgery yields superior results as an integral treatment modality in patients with single or limited BMs from MM. In the second scenario, patients present with a solitary brain lesion in the setting of synchronous extracranial disease. Our study shows that both surgical resection and CK SRS can be offered to this patient group. However, OS in these patients remains short because of the presence and usual progression of the systemic disease. In the third and fourth scenarios, patients present with multiple BMs, either with or without evidence of extracranial metastasis. In these scenarios, with the OS in the salvage setting after probably appropriate WBRT upfront, it is speculative if elective SRS in these patients could have affected their outcome, at least in patients with limited metastasis. However, the overall LCR is very limited in patients undergoing prior WBRT, as was the case in our patient cohort. Patients with multiple lesions who received WBRT often recur in one to few lesions who are then treated with SRS. It is unclear why the local control is poorer in this case even though there was no difference in delivered SRS dose.

Limitations of this study

Bernard *et al.* have pointed out that studies of this format always suffer from the common biases present in retrospective analyses and moreover mentioned several shortcomings which constitute problems for our study as well.[3] In particular, the selected patient groups were treated with varying treatment modalities, the conclusions on the most relevant prognostic pretreatment factors remain difficult to assess. For example, small numbers in subgroups of patients with single brain metastasis and controlled systemic disease among various treatment groups makes it difficult to extrapolate optimal outcomes in specific circumstances. In addition, only 92% of the patients analyzed in this study had complete follow-up images available for review. The remainder of the cohort transferred care to other facilities and could not be evaluated. The patient cohort presented here, albeit reasonable in number, has received fairly different therapeutic regimens to manage their intra- and extracranial disease manifestations. This makes it difficult to isolate the impact of the various CNS-treatment modalities until much larger case series have been analyzed or until specific and prospective treatment algorithms will accrue sufficient numbers to arrive at more definite conclusions with respect to outcome determinants.

CONCLUSIONS

Over the recent years, the shortcomings of WBRT in the treatment of BM from MM have become apparent. At the same time, SRS is evolving as a widely available treatment approach that provides effective and safe treatment of BM at acceptable levels of toxicity. While initial SRS and surgery offer different treatment modalities for the same patient population, this study suggests that surgery remains the cornerstone in the treatment of patients with large BM from MM, as it has been shown to lead to excellent tumor control rates and potentially improved survival. However, technical advances of SRS and earlier detection of small and even clinically asymptomatic lesions make primary SRS increasingly an attractive choice for the management of patients with single or very few BMs. Our study and others indicate that initial surgery may play a crucial role to the addition of SRS for improving local control, neurological status and even OS in patients with symptomatic BMs from MM. This deserves further study either through a randomized controlled trial or through nonrandomized parallel group studies or studies of controlled interrupted-time series.

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