ANTICANCER RESEARCH *36*: 5333-5338 (2016)
doi:10.21873/anticanres.11106

Pro-inflammatory State Portends Poor Outcomes with Stereotactic Radiosurgery for Brain Metastases

NAREK SHAVERDIAN[1], JASON WANG[1], REBECCA LEVIN-EPSTEIN[1], DORTHE SCHAUE[1], PATRICK KUPELIAN[1], PERCY LEE[1], ISAAC YANG[2] and TANIA KAPREALIAN[1]

[1]*Department of Radiation Oncology, University of California Los Angeles, Los Angeles, CA, U.S.A.;*
[2]*Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA, U.S.A.*

Abstract. *Aim: We determined if pre-treatment systemic inflammation would predict poor outcomes in the setting of stereotactic radiosurgery (SRS) for brain metastases. Patients and Methods: The pretreatment albumin concentration, neutrophil and lymphocyte counts, and the platelet-to-lymphocyte ratio (PLR) were evaluated to determine association with intracranial control, local control (LC), initial MRI response (MR), and overall survival (OS) among 70 patients with 152 separate brain metastases treated with SRS alone from 2008-2015. Results: On multivariate analysis, a higher neutrophil percentage predicted for poor LC, poor initial MR, poor OS and poor intracranial control (p=0.01, p=0.01, p=0.02 and p=0.03, respectively). A lower percentage of lymphocytes predicted for poor LC and poor MR (p=0.01 and p=0.02), and an elevated PLR predicted for poor OS and poor LC (p=0.05 and p=0.04). Additionally, a lower pretreatment albumin concentration predicted for poor LC and OS (p=0.01 and p=0.03). Conclusion: Pretreatment systemic inflammation is associated with poor outcomes post-SRS.*

Metastatic brain tumors are the most common intracranial neoplasms, with an incidence that continues to rise as a result of advances in neuroimaging and more effective systemic therapies. Population-based studies suggest that up to 45% of all patients with cancer develop brain metastases and that the majority of brain metastases originate from lung cancer, breast cancer and melanoma (1). The standard-of-care for brain metastases continues to evolve given innovations in radiation technology, surgical techniques and systemic therapies. However, among patients not requiring surgical resection, stereotactic radiosurgery (SRS) represents an effective and favored treatment modality with high rates of local control (2-4).

Pre-treatment markers of systemic inflammation, including an elevated platelet-to-lymphocyte ratio (PLR), elevated neutrophil count, low lymphocyte count and low serum albumin concentration, have been found to predict responses to anti-neoplastic therapies and disease outcomes across multiple different malignancies (5-11). However, these markers and the role the systemic immune system plays in treatment outcomes in the setting of SRS for brain metastases have yet to be fully evaluated. There is a growing use of immunotherapy among patients with advanced cancer, and recent studies are suggesting improvements in outcomes with the combination of SRS and immunotherapy with checkpoint inhibition for treatment of brain metastases (12). Therefore, further exploring the role the systemic immune system plays in brain radiosurgery outcomes is now essential.

Although the blood–brain barrier selectively isolates the central nervous system, circulating systemic immune cells are capable of migrating from the cerebral vessels into the brain parenchyma in response to various stimuli (13). Additionally, multiple studies have established that there is substantial cross-talk between systemic immune responses and inflammatory cells in the brain (14, 15). Interestingly, pathological studies on brain metastases post-SRS have identified an inflammatory cellular response to be characteristic, suggesting an interaction between the immune system and SRS outcomes (16). We therefore sought to further evaluate the relationship between outcomes brain SRS and immune responses. We determined if pretreatment immune parameters associated with systemic inflammation would predict the initial response to SRS seen on the first post-treatment magnetic resonance imaging (MRI), and for local control, distant intracranial control and overall survival in the setting of SRS for brain metastases.

Correspondence to: Tania Kaprealian, MD, UCLA Department of Radiation Oncology, 200 UCLA Medical Plaza, Suite B265, Los Angeles, CA 90095-6951, CA, U.S.A. Tel: +1 3108259771, Fax: +1 3107949795, e-mail: TKaprealian@mednet.ucla.edu

Key Words: Brain metastases, radiosurgery, SRS, immune responses, inflammation.

Patients and Methods

Patients. Records of consecutive patients with a first occurrence of metastatic brain disease, with a single brain metastasis or multiple brain metastases, from either non-small cell lung cancer (NSCLC), breast cancer or melanoma treated with stereotactic radiation alone from 2009-2015 at a tertiary medical center were included. Patients were seen initially in a multidisciplinary setting with a radiation oncologist and neurosurgeon, and were recommended to proceed with SRS alone. In order to prevent confounding with prior and other therapies, patients with any prior brain radiation or brain surgery were excluded, as were patients who received combination whole-brain radiation and SRS. The study was approved by our Institutional Review Board (12-001760-CR-00002), and retrospectively acquired data were de-identified according to the Health Insurance Portability and Accountability Act guideline (17).

Treatment. Brain metastases were identified using MRI. MRIs with 1-mm thickness image slices were fused with computed tomographic (CT) simulation imaging for target localization and treatment planning. The gross tumor volume (GTV) was then contoured and an additional margin of 1 mm was added to create the planning target volume (PTV). All brain metastases were treated with SRS in a single session. SRS doses were based on institutional practices, and were 14, 16 or 18 Gy. The dose was prescribed to maintain the total volume of brain receiving 12 Gy to be less than 10 cc. Treatment plans were evaluated to ensure coverage of 100% of the PTV with the prescription dose, allowing for hotspots of up to 120% in the target. Treatment delivery was linear accelerator-based and image guidance was provided with the Brainlab ExacTrac position system (BrainlabAG, Feldkirchen, Germany). Additionally, patients did not receive any systemic anti-neoplastic therapy within at least a 1-2 week window from the timing of SRS.

Immune parameters. The serum albumin level, and peripheral lymphocyte and neutrophil counts and their relative percentages for each patient were taken from the most proximal complete blood count and metabolic panel drawn within two weeks prior to the delivery of radiation therapy. The PLR was then calculated from these values. These immune parameters were then evaluated as continuous variables in statistical analyses.

Follow-up. Patients were followed-up at interval examinations by their treating radiation oncologist/medical oncologists at 2- to 3-month intervals. MRI was routinely obtained at 2- to 3-month intervals post-treatment and was reviewed by dedicated neuroradiologists allowing for a multidisciplinary assessment of true progression *vs*. pseudoprogression. The initial MRI response was based on the first 2-3-month post-treatment MRI. Treatment responses were categorized as local failure or progressive disease (PD) if there was a persistent ≥20% increase in size of the irradiated lesion on subsequent MRIs per Response Evaluation Criteria in Solid Tumors (RECIST) (18). Partial response (PR) was defined as at least a 30% decrease in the size of the irradiated lesion, complete response (CR) was defined as no evidence of the target lesion, and stable disease (SD) was defined as a lesion that did not qualify as either a PD or PR per RECIST criteria (18). Intracranial failure was defined as the development of a new brain metastasis in a different, not previously irradiated location.

Table I. *Baseline patient characteristics (n=70) at the time of initial treatment*.

Factor	Value
Median age (range), years	62 (41-90)
Gender, n (%)	
Male	36% (25)
Female	64% (45)
Primary, n (%)	
NSCLC	60% (42)
Breast	19% (13)
Melanoma	21% (15)
KPS, n (%)	
100	12% (8)
90	67% (47)
80	14% (10)
70	7% (5)
Median no. brain metastases (range)	2 (1-7)
Brain metastasis burden	
Single	46% (32)
More than 1	54% (38)
Median volume brain metastases (range), cc	
Mean	0.41 (0.13-9.26)
Mean volume, cc	1.4
Extracranial disease control, n (%)	
Yes	33% (23)
No	67% (47)
Pretreatment steroids, n (%)	
Yes	23% (19)
No	77% (51)
Median follow-up (range), months	14.7 (3.1-91.2)

NSCLC: Non-small cell lung cancer; KPS: Karnofsky Performance Status.

Table II. *Pre-treatment patient immune parameters at the time of treatment*.

Factor	Value
Median albumin (range), g/dl	4.1 (2.90-5.1)
Median neutrophils (range), %	65.20 (35.4-92.6)
Median lymphocytes (range), %	22.4 (3.4-47.20)
Median PLR (range)	204.82 (59.23-747.50)

PLR: Platelet:lymphocyte ratio.

Statistical analysis. Kaplan–Meier analysis was used to estimate the 1-year local control, intracranial control, and overall survival rates of our patient population. Pre-treatment immune parameters serum albumin level, neutrophil percentage, lymphocyte percentage, and PLR were evaluated continuously in a univariate Cox proportional hazards model to determine any association with local failure, intracranial failure and overall survival. It was similarly determined if these pre-treatment immune parameters would predict either a CR or PR of the irradiated brain metastases on the initial post-treatment MRI *vs*. SD or PD. A multivariate Cox proportional hazards model was then created which adjusted for age, Karnofsky performance

Table III. *Univariate analysis of pre-treatment markers of systemic inflammation and stereotactic radiosurgery outcome.*

	Hazard ratio (*p*-value)			
Factor	Initial MR response*	Local failure	Intracranial failure	Overall survival
Albumin	0.39 (p=0.13)	**0.12 (p<0.01)**	0.53 (p=0.15)	**0.39 (p=0.01)**
Neutrophil %	**1.06 (p<0.01)**	**1.06 (p=0.02)**	1.01 (p=0.34)	**1.03 (p=0.05)**
Lymphocyte %	**0.93 (p=0.01)**	**0.93 (p=0.04)**	0.98 (p=0.49)	0.97 (p=0.09)
PLR	1.01 (p=0.27)	**1.01 (p=0.03)**	**1.01 (p=0.04)**	**1.01 (p=0.03)**

MR: Magnetic resonance imaging, PLR: platelet:lymphocyte ratio. *Complete or partial response *vs*. stable or progressive disease. Significant values shown in bold.

Table IV. *Multivariate analysis of pre-treatment markers of systemic inflammation and stereotactic radiosurgery outcome.*

	Hazard ratio (*p*-value)			
Factor	Initial MR response*	Local failure	Intracranial failure	Overall survival
Albumin	0.50 (p=0.30)	**0.08 (p=0.01)**	0.54 (p=0.24)	**0.29 (p=0.03)**
Neutrophil %	**1.07 (p=0.01)**	**1.06 (p=0.01)**	**1.03 (p=0.02)**	**1.03 (p=0.03)**
Lymphocyte %	**0.92 (p=0.02)**	**0.93 (p=0.03)**	0.97 (p=0.12)	0.97 (p=0.16)
PLR	1.01 (p=0.38)	**1.01 (p=0.04)**	**1.01 (p=0.06)**	**1.01 (p=0.04)**

MR: Magnetic resonance imaging. *Complete or partial response *vs*. stable or progressive disease. Multivariate model adjusted for age, Karnofsky Performance Status, number of brain metastases, and pre-treatment steroid use. Significant values shown in bold.

status (KPS), number of brain metastases, and pre-treatment steroid use to determine if these pre-treatment immune parameters would independently predict outcome. Patients were censored from further analysis at the time of local and/or intracranial failure. Analysis was performed using SAS version 9.4 (SAS Institute, NC, USA) and a value of $p \leq 0.05$ was considered statistically significant.

Results

Patient characteristics. Seventy consecutive patients with initial presentation of metastatic brain disease treated between 2009 and 2015 with 152 separate brain metastases were analyzed with a median post-treatment follow-up of 14.7 months. Ninety-five percent (n=145) of all lesions were treated with 16 Gy or 18 Gy SRS. The remaining seven metastases received 14 Gy SRS. Baseline patient characteristics are shown in Table I. The majority of patients (64%) were female and the median patient age was 62 years. The majority of patients had primary NSCLC (60%), followed by 21% with melanoma, and 19% with primary breast cancer. Seventy-nine percent of patients had either a baseline KPS of 90 or 100. Seventy-seven percent of patients were not on steroids at the time of treatment. Forty-six percent of patients had a single brain metastasis. The median number of brain lesions per patient was two (range: 1-7), the median brain metastasis volume was 0.41 cc, with a range from 0.13 cc to 9.26 cc.

The 1-year overall survival rate for patients overall was 67%, and the 1-year local and intracranial control rates were 77% and 52%, respectively. Of the 70 patients evaluated, pre-treatment immune parameters were available for 89% (n=62) and are shown in Table II.

Pre-treatment immune profile and effects on SRS outcome and overall survival. On univariate analysis, patients with markers consistent with pre-treatment systemic inflammation, namely a higher pre-treatment neutrophil percentage, lower lymphocyte percentage, higher PLR and lower serum albumin concentration were more likely to have local failure of their irradiated brain metastases (p=0.02, p=0.04, p=0.03 and p<0.01, respectively). Furthermore, patients with a higher percentage of neutrophils and a lower percentage of lymphocytes were statistically more likely to have progression or stability of their irradiated brain metastases on their initial 2- to 3-month post-treatment MRI *vs*. a CR or PR (p<0.01 and p=0.01, respectively). Additionally, a higher pre-treatment PLR predicted a subsequent intracranial failure on univariate analysis (p=0.04). A lower serum albumin concentration, higher neutrophil percentage, and higher PLR also predicted a shorter overall survival (p=0.01, p=0.05 and p=0.03, respectively) (Table III).

On multivariate analysis after adjusting for age, KPS, number of brain metastases and pre-treatment steroid use, all indices of pre-treatment systemic inflammation namely a lower serum albumin concentration, higher percentage of neutrophils, lower percentage of lymphocytes, and higher PLR, independently predicted local failure of the irradiation to brain metastases on multivariate analysis (p=0.01, p=0.01, p=0.03, and p=0.04, respectively). Furthermore, a higher percentage of neutrophils and a lower percentage of lymphocytes continued to predict progression or stability of the irradiation brain metastases on the initial 2- to 3-month post-treatment MRI *vs.* a CR or PR (p=0.01 and p=0.02, respectively). A higher percentage of neutrophils predicted subsequent intracranial failure (p=0.02), and higher PLR trended in significance for predicting subsequent intracranial failure (p=0.06). Additionally, a lower pre-treatment albumin level, higher percentage of neutrophils, and higher PLR all independently predicted poor overall survival on multivariate analysis (p=0.03, p=0.03, and p=0.05 respectively) (Table IV).

Discussion

Brain metastases are the most common intracranial tumors with an incidence that continues to rise, especially as systemic treatment options improve and life expectancy increases. SRS is a preferred treatment option for patients that do not require surgery and offers high rates of tumor control. Immune responses have been found to play a role in modulating the effects of anticancer treatments across many different malignancies, but little is known of their role in the setting of brain SRS. As far as we are aware of, we are the first to show that pre-treatment immune markers of systemic inflammation are independent prognostic factors for outcomes in the setting of SRS for brain metastases. We found that pre-treatment markers associated with systemic inflammation predicted local failure post-SRS. Specifically, we found on multivariate analysis that a higher pre-treatment neutrophil percentage, lower lymphocyte percentage, and higher PLR predict local failure post brain SRS. Furthermore, we found pre-treatment markers of systemic inflammation including a higher neutrophil percentage, and lower lymphocyte percentage to predict against a CR or PR to radiosurgery on the initial post-treatment brain MRI. Additionally, our data suggests that pre-treatment systemic inflammation predicts distant intracranial failure post-SRS, with a higher pre-treatment neutrophil percentage predicting subsequent intracranial failure. While previous data have shown markers of systemic inflammation to predict poor survival among patients with advanced cancer, our data evaluated local and intracranial control post-SRS, and suggest that immune responses play a greater role in modulating outcomes of brain SRS.

An elevated pre-treatment PLR, neutrophilia, lymphopenia and hypoalbuminemia are all markers of systemic inflammation that have been found to predict disease and treatment outcomes in multiple different types of cancer. Specifically, pretreatment lymphopenia has been found to predict a poor response to chemotherapy in the setting of lung, breast and colorectal cancer (8). An elevated pre-treatment PLR has been shown to predict poor outcome in the setting of SRS for early-stage NSCLC. Furthermore, hypoalbuminemia has been validated to serve as a marker for systemic inflammation (11), and is found to predict disease recurrence after complete resection of early-stage NSCLC (9, 10). Therefore, although novel in the setting of brain SRS, our finding that markers of systemic inflammation prior to SRS predict poor outcome is supported by these previous data in different treatment settings.

The radiobiological mechanisms behind radiosurgery have yet to be fully elucidated, but a combination of direct cytotoxic effects and vascular changes have been implicated (19). Histological analyses of brain metastases after radiosurgery are limited, but pathological studies have shown an inflammatory reaction made up of an accumulation mostly of leukocytes to be a characteristic response to SRS (16). Furthermore, it has been found on pathology review that tumors that failed to respond to SRS had either no inflammatory reaction or only a minimal inflammatory reaction following treatment (16). Therefore, it has been postulated that this inflammatory response plays an important role in tumor control following SRS (16). These pathological findings are very compelling as they support our data that immune responses play a role and modulate the effects of brain SRS. Potentially, pre-treatment systemic inflammation allows for immune dysregulation and prevents the development of this inflammatory response that has been postulated to be important for tumor control following SRS. Furthermore, the improved outcomes suggested by the combination of checkpoint inhibition and brain SRS may potentially be secondary to a bolstered immune system mounting a greater inflammatory response post SRS (20).

While this study comprehensively evaluated multiple key immunological parameters and provides novel insights into the role of the systemic immune system in outcomes of SRS for brain metastases, it is limited by its retrospective nature, which creates inherent bias. Another limitation is that although the vast majority of patients had laboratory draws prior to SRS, they were not always collected for all patients. However, we present a fairly homogeneous dataset of patients treated with SRS alone on initial presentation of metastatic brain disease in a tertiary medical center, and provide novel evidence on the role systemic inflammation and the immune system play on brain radiosurgery outcomes. With the growing evidence that immune responses modulate brain SRS outcomes, further exploring

combinations of immunotherapies and SRS may allow for improved clinical outcomes. These data can help further stratify patients with brain metastases, and select patients who may benefit from the combination of radiosurgery and immunotherapy with checkpoint inhibition.

In conclusion, we found that pretreatment immune markers of systemic inflammation, namely a higher PLR, higher neutrophil percentage, lower lymphocyte percentage and lower serum albumin concentration, predict poor outcome after SRS for brain metastases. These data suggests that the systemic immune system plays a significant role in modulating responses to brain radiosurgery and therefore warrant further clinical investigation.

Conflicts of Interest

There are no conflicts of interest from any Authors.

References

1 Gavrilovic IT and Posner JB: Brain metastases: epidemiology and pathophysiology. J Neurooncol *75(1)*: 5-14, 2005.

2 Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn Ca and Chang EL: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol *2(3)*: 210-225, 2012.

3 Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, Robinson PD,Ammirati M, Cobbs CS, Gaspar LE, Loeffler JS, McDermott M, Mehta MP, Mikkelsen T, Olson JJ, Paleologos NA, Patchell RA, Ryken TC and Kalkanis SN: The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol *96(1)*: 45-68, 2010.

4 Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Watanabe S and Kasuya H: Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 *versus* 10 or more tumors. J Neurosurg *121 Suppl*: 16-25, 2014.

5 Liu H, Wu Y, Wang Z, Yao Y, Chen F, Zhang H, Wang Y and Song Y: Pretreatment platelet-to-lymphocyte ratio (PLR) as a predictor of response to first-line platinum-based chemotherapy and prognosis for patients with non-small cell lung cancer. J Thorac Dis *5(6)*: 783-789, 2013.

6 Bhatti I, Peacock O, Lloyd G, Larvin M and Hall RI: Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte *versus* platelet-lymphocyte ratio. Am J Surg *200(2)*: 197-203, 2010.

7 Teramukai S, Kitano T, Kishida Y, Kawahara M, Kubota K, Komuta K, Minato K, Mio T, Fujita Y, Yonei T, Nakano K, Tsuboi M, Shibata K, Furuse K and Fukushima M: Pretreatment neutrophil count as an independent prognostic factor in advanced non-small-cell lung cancer: an analysis of Japan Multinational Trial Organisation LC00-03. Eur J Cancer *45(11)*: 1950-1958, 2009.

8 Lissoni P, Brivio F, Fumagalli L, Messina G, Ghezzi V, Frontini L, Giani L, Vaghi M, Ardizzoia A and Gardani GS: Efficacy of cancer chemotherapy in relation to the pretreatment number of lymphocytes in patients with metastatic solid tumors. Int J Biol Markers *19(2)*: 135-140, 2004.

9 Jin Y, Zhao L and Peng F: Prognostic impact of serum albumin levels on the recurrence of stage I non-small cell lung cancer. Clinics (Sao Paulo) *68(5)*: 686-693, 2013.

10 Shaverdian N, Veruttipong D, Wang J, Schaue D, Kupelian P and Lee P: Pretreatment immune parameters predict for overall survival and toxicity in early-stage non-small-cell lung cancer patients treated with stereotactic body radiation therapy. Clin Lung Cancer *17(1)*: 39-46, 2016.

11 Don BR and Kaysen G: Serum albumin: relationship to inflammation and nutrition. Semin Dial *17(6)*: 432-437, 2004.

12 Ahmed KA, Stallworth DG, Kim Y, Johnstone PA, Harrison LB, Caudell JJ, Yu HH, Etame AB, Weber JS and Gibney GT: Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. Ann Oncol *27(3)*: 434-441, 2016.

13 Hamilton A and Sibson NR: Role of the systemic immune system in brain metastasis. Mol Cell Neurosci *53(3)*: 42-51, 2013.

14 McColl BW, Rothwell NJ and Allan SM: Systemic inflammatory stimulus potentiates the acute phase and CXC chemokine responses to experimental stroke and exacerbates brain damage *via* interleukin-1- and neutrophil-dependent mechanisms. J Neurosci *27(16)*: 4403-4412, 2007.

15 Serres S, Anthony DC, Jiang Y, Broom KA, Campbell SJ, Tyler DJ, van Kasteren SI, Davis BG and Sibson NR: Systemic inflammatory response reactivates immune-mediated lesions in rat brain. J Neurosci *29(15)*: 4820-4828, 2009.

16 Szeifert GT, Atteberry DS, Kondziolka D, Levivier M and Lunsford LD: Cerebral metastases pathology after radiosurgery: a multicenter study. Cancer *106(12)*: 2672-2681, 2006.

17 The Health Insurance Portability and Accountability Act of 1996. Pub. L. 104-191. Stat. 1936 (1996).

18 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45(2)*: 228-247, 2009.

19 Kondziolka D, Shin SM, Brunswick A, Kim I and Silverman JS: The biology of radiosurgery and its clinical applications for brain tumors. Neuro Oncol *17(1)*: 29-44, 2015.

20 Silk AW, Bassetti MF, West BT, Tsien CI and Lao CD: Ipilimumab and radiation therapy for melanoma brain metastases. Cancer Med *2(6)*: 899-906, 2013.

Received September 9, 2016
Revised September 20, 2016
Accepted September 23, 2016