Published in final edited form as:

J Neurooncol. 2018 September ; 139(3): 689–697. doi:10.1007/s11060-018-2914-5.

Post-treatment neutrophil-to-lymphocyte ratio predicts for overall survival in brain metastases treated with stereotactic radiosurgery

Mudit Chowdhary¹, Jeffrey M. Switchenko², Robert H. Press³, Jaymin Jhaveri³, Zachary S. Buchwald³, Philip A. Blumenfeld¹, Gaurav Marwaha¹, Aidnag Diaz¹, Dian Wang¹, Ross A. Abrams¹, Jeffrey J. Olson⁴, Hui-Kuo G. Shu³, Walter J. Curran³, and Kirtesh R. Patel⁵

¹Department of Radiation Oncology, Rush University Medical Center, 500 South Paulina, Chicago, IL 60612, USA

²Biostatistics and Bioinformatics Shared Resource, Winship Cancer Institute, Emory University, Atlanta, GA, USA

³Department of Radiation Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, USA

⁴Department of Neurosurgery, Winship Cancer Institute, Emory University, Atlanta, GA, USA

⁵Department of Therapeutic Radiology and Smilow Cancer Center, Yale School of Medicine, 333 Cedar Street, New Haven, CT 06510, USA

Abstract

Introduction—Neutrophil-to-lymphocyte ratio (NLR) is a surrogate for systemic inflammatory response and its elevation has been shown to be a poor prognostic factor in various malignancies. Stereotactic radiosurgery (SRS) can induce a leukocytepredominant inflammatory response. This study investigates the prognostic impact of post-SRS NLR in patients with brain métastases (BM).

Methods—BM patients treated with SRS from 2003 to 2015 were retrospectively identified. NLR was calculated from the most recent full blood counts post-SRS. Overall survival (OS) and intracranial outcomes were calculated using the Kaplan-Meier method and cumulative incidence with competing risk for death, respectively.

Results—188 patients with 328 BM treated with SRS had calculable post-treatment NLR values. Of these, 51 (27.1%) had a NLR >6. The overall median imaging follow-up was 13.2 (14.0 vs. 8.7 for NLR ≤ 6.0 vs. >6.0) months. Baseline patient and treatment characteristics were well balanced, except for lower rate of ECOG performance status 0 in the NLR > 6 cohort (33.3 vs. 44.2%, $p = 0.026$). NLR >6 was associated with worse 1- and 2-year OS: 59.9 vs. 72.9% and 24.6 vs. 43.8%, ($p = 0.028$). On multivariable analysis, NLR > 6 (HR: 1.53; 95% CI 1.03–2.26, $p = 0.036$) and

Mudit Chowdhary mchowdharymd@gmail.com, Kirtesh R. Patel kirtesh@gmail.com.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Portions of this work were presented at the European Society for Radiotherapy & Oncology 2018 Annual Meeting on April 21, 2018 in Barcelona, Spain.

presence of extracranial metastases (HR: 1.90; 95% CI 1.30–2.78; $p < 0.001$) were significant predictors for worse OS. No association was seen with NLR and intracranial outcomes.

Conclusion—Post-treatment NLR, a potential marker for post-SRS inflammatory response, is inversely associated with OS in patients with BM. If prospectively validated, NLR is a simple, systemic marker that can be easily used to guide subsequent management.

Keywords

Brain metastases; Stereotactic radiosurgery; Neutrophil-to-lymphocyte ratio; Immune response; Survival

Introduction

Brain metastases (BM) are the most common intracranial tumor, with nearly 30% of all cancer patients developing intracranial involvement [1]. The incidence of BM is steadily increasing, in part due to increased surveillance and improvements in systemic extracranial therapy [2, 3]. The standard of care for BM continues to evolve given advancements in focal therapies, including stereotactic radiosurgery (SRS), which can offer a high rate of local control without the consequences of whole brain radiotherapy (WBRT) [4]. Nonetheless, despite these treatments, overall survival (OS) remains relatively dismal.

For BM patients, prognostic models have been utilized to predict patient outcomes. Recursive prognostic analyses [5] and graded prognostic analyses (GPA) are scoring systems that incorporate multiple baseline patient factors to predict survival [6, 7]. However, as patients are living longer and receiving newer therapies, including targeted and immune therapy with SRS, further models are needed to stratify patients.

Recently, Hannahan et al. updated their seminal review paper on carcinogenesis [8], now incorporating the inflammatory process and immune system as modulators [9]; markers of these systems include neutrophil and lymphocytes, and. As such, multiple investigators have shown that elevated neutrophil-to-lymphocyte ratio (NLR) is associated with worse outcomes in multiple malignancies [10–12]. While the blood brain barrier can limit intracranial penetration of non-lipophilic molecules, recent evidence suggests inflammatory cells are able to cross into the brain [13]. Consistent with these reports, Bambury [14] and Mason et al. [15] have also shown that pre-operative NLR also predicts OS in glioblastoma.

The aim of this study is to now investigate the association of NLR and OS in BM patients. Because radiotherapy can cause an inflammatory response and possibly modulate the NLR, this initiative will focus only on BM treated with SRS alone.

Materials and methods

Patient selection

After receiving Institutional Review Board approval, records of patients with a first occurrence of metastatic intracranial disease, from any histology, who were treated with SRS

from 2003 to 2015 were examined at multiple institutions. Patients who were treated with any prior brain irradiation or combination WBRT + SRS were excluded, as were patients with radiosensitive malignancies (e.g. small cell, germ cell, and lymphoma). NLR were calculated based on peripheral lab values identified within 1 month of SRS, while patients with missing values were excluded. Patients were also considered ineligible if they were found to have a coincident infectious process at time of lab draw.

Baseline characteristics were extracted from patient charts including age, sex, primary histology, Eastern Cooperative Group Oncology performance status (ECOG PS), active systemic disease, presence of extracranial metastases, GPA, total number of BM, aggregate BM volume, resection status, corticosteroid use and pre and post-SRS systemic therapy use (chemotherapy, targeted, and immunotherapy). Baseline treatment parameters were also recorded including BM laterality, BM location, gross tumor volume (GTV), planning target volume (PTV), SRS total dose, number of fractions, dose/fraction, prescription isodose line (IDL), and conformality index.

Stereotactic radiosurgery

SRS was delivered using a linear accelerator with 6 MV photon energies, as described previously [16, 17]. All BM underwent patients underwent high-resolution treatment planning magnetic resonance imaging (MRI) scan with and without contrast within 10 days of computed tomography simulation. The T1 MRI contrast enhancing tumor defined lesion constituted the GTV. For resected brain cavities, the GTV also included the resection cavity. The GTV was expanded by 1.0–2.5 mm to generate the PTV, based on treating physician preference, with a larger margin utilized for resection cavities. Doses prescribed were based on size as per Radiation Therapy Oncology Group 90–05 [18]: PTVs that were 2.0 cm in diameter were typically treated to 21 Gy, 2.1–3.0 cm in diameter to 18 Gy, and 3.1–4.0 cm in diameter to 15 Gy. For BM larger than 4.0 cm in maximum diameter, fractionated SRS delivering 21–30 Gy over 3–5 treatments, with a frameless radiosurgery technique was utilized.

Follow-up

After treatment with SRS, follow-up consisted of history, clinical examination and brain MRI at 1 month and then at every 3 months thereafter, unless clinically indicated at an earlier time point. Local recurrence (LR) was defined as the presence of new progressive nodular enhancement within the prior 80% IDL of the prior SRS treatment, while distant brain recurrence (DBR) was any recurrence outside the 80% IDL. Radiographic radiation necrosis (RN) was defined as development of a contrast-enhancing mass within prior SRS fields [19]; if there was a question of the nodular enhancement representing LR vs. RN, cases were discussed at a multi-disciplinary tumor board to develop a consensus. Additional functional imaging was also obtained (e.g. MR perfusion, MR spectroscopy, or brain positron emission tomography [PET]) to further aid evaluation. Leptomeningeal disease (LMD) was defined as new leptomeningeal enhancement seen on post-contrast T1 MRI sequences.

Statistical analysis

NLR was analyzed as a continuous and dichotomous variable. Similar to prior analyses, the cut-point which provided the strongest prognostic information in our dataset was used for analysis as a dichotomous variable [14, 20]. This was determined by testing a range of possible cut-points (range 2.0–6.0 based on prior publications) and seeing which had the most significant p value associated with OS.

The high and low-NLR cohorts were then compared across categorical covariates using Fisher's Exact test or Chi-squared tests, where appropriate, and were compared across continuous variables using ANOVA. For OS, death from any cause was defined as the event, and patients were censored at time of last follow-up. Kaplan–Meier product limit method was utilized to estimate OS; the log-rank test was used to assess for differences between with high NLR and low-NLR groups. Univariate analysis (UVA) and multivariate analysis (MVA) were performed using the Cox proportional hazards model.

To estimate rates of intracranial outcomes—LR, DBR, RN, and LMD—the cumulative incidence methodology, with death without the event considered a competing risk was used. For these intracranial outcomes, patients were censored at time of last brain imaging. Cumulative incidence curves for each non-survival outcome were compared using Gray's test for equality across groups [21]. UVA and MVA were performed using the semiparametric proportional hazards model in the presence of competing risks, as proposed by Fine and Gray [21]. All potentially prognostic covariates which were statistically significant in the UVA were entered into the MVA model. All statistical tests were two-sided, with p values < 0.05 considered statistically significant. Statistical analysis was carried out using SAS version 9.4.0 statistical software (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics

A total of 188 consecutive patients with 328 BM with calculable NLR were identified. Median and mean NLR was 3.53 and 6.39, respectively; the range of NLR was 0.61–88.00. When analyzing NLR as a categorical, dichotomous variable, a cut-off point of six provided the strongest prognostic value; in this study the NLR cohorts were therefore set as > 6 and ≤ 6.

51 (27.1%) patients with 95 (29.0%) BM had NLR > 6 post-SRS. The baseline patient (Table 1) characteristics were similar between the two groups, including rates of corticosteroid use and pre- and post-SRS systemic therapy (chemo, targeted, and immunotherapy), except that the NLR > 6 cohort had a lower rate of ECOG performance status 0 (33.3 vs. 44.5%, p = 0.026). No differences were seen in baseline lesion-level (Table 1) treatment characteristics between the two cohorts. None of the patients that were reviewed had a coincident infectious process. The median imaging follow-up was 13.2 months for all patients, 14.0 months for NLR ≤ 6.0, and 8.7 months for NLR > 6.0.

Overall survival

The median OS for the entire cohort was 19.1 months. Median OS was longer in the cohort with a post-treatment NLR ≤ 6 , 20.7 (range 17.4–25.5) months, as compared to the cohort with NLR > 6 , 14.7 (range 10–16.8) months. Figure 1 illustrates the higher 1- and 2-year OS rates in the post-treatment NLR ≤ 6 cohort: 72.9 vs. 59.9% and 43.8 vs. 24.6% ($p = 0.028$). On UVA, (Table 2) NLR [Hazard ratio (HR): 1.52; 95% confidence interval (CI) 1.04–2.21; $p = 0.028$], presence of extracranial metastases (HR: 1.93; 95% CI 1.38–2.69, $p < 0.001$), and GPA (HR: 0.46; 95% CI 0.23–0.93, $p = 0.036$) were statistically significant predictors for OS. On MVA (Table 3), both NLR > 6 (HR: 1.53; 95% CI 1.03–2.26, $p = 0.036$) and presence of extracranial metastases (HR: 1.90; 95% CI 1.30–2.78; $p < 0.001$) were statistically significant predictors for worse OS.

Intracranial outcomes

No difference in intracranial outcomes was seen between the two cohorts. LR was observed in 54 (16.5%) of irradiated lesions/cavities: 1-year rates of LR was 10.5% for NLR ≤ 6 and 12.0% for NLR > 6 ($p = 0.373$). DBR occurred in 126 (67.0%) of patients: 1-year rates of DBR was higher for the NLR > 6 cohort, 59.0 vs. 49.8%, though the results were not statistically significant ($p = 0.370$). RN occurred in 89 (27.1%) lesions/cavities post-SRS: 1-year rates of RN for NLR > 6 and ≤ 6 was 16.4 and 14.3% ($p = 0.982$), respectively. There was no difference in 1-year rates of LMD: 12.2% for NLR > 6 and 5.9% for NLR ≤ 6 ($p = 0.971$).

Discussion

The link between inflammation, particularly chronic inflammation, and cancer progression is well known. While the exact biology behind the role of elevated NLR in cancer prognosis remains to be fully elucidated, it is considered a marker of systemic inflammation that may portend a worse prognosis by driving cancer cell proliferation through increasing availability of growth, angiogenic, and other pro-neoplastic factors [9]. The effect of systemic inflammation on white blood cells typically displays a rise in neutrophils with a concomitant drop in lymphocytes, which may be caused by increased margination and apoptosis of these cells [22]. This loss of cell-mediated immunity may also play a role in the biology of this phenomenon. Neutrophilia as an inflammatory response is known to inhibit the cytolytic activity of activated T cells and natural killer cells [23, 24]. Additionally, neutrophils have been reported to secrete tumor growth promoting factors, including vascular endothelial growth factor [25], hepatocyte growth factor [26], IL-6 [27], matrix metalloproteinases [28], and elastases [29] that likely contribute to a tumor stimulating microenvironment. Conversely, a high percentage of circulating lymphocytes is associated with better tumor response and outcome as a result of an augmented antitumor lymphocyte effect [30].

In this study, we investigated the hypothesis that NLR is associated with OS for patients with BM treated with SRS. Our analyses revealed that the optimal NLR cut-off associated with OS was 6; OS was statistically significantly lower in patients with NLR > 6 compared to less ≤ 6 : 59.9 vs. 72.9%. NLR did not correlate with intracranial outcomes, including LR, DBR and RN.

Numerous other studies have investigated the optimal NLR in a variety of malignancies [10–12, 14, 15]. The dichotomous cut point used for NLR to best predict OS has ranged from 2.18 to 7.5. Consistent with our findings, all of these studies have demonstrated that the lower NLR value is associated with higher OS. Our study differs from these analyses in that we examined post-treatment NLR levels rather than pre-treatment values. Pre-clinical evidence suggests that radiation can enhance antigen presentation and release cytokines, including IFN- γ , that help recruit, activate, and increase lymphocytes [31, 32]; tumors that demonstrate a low NLR may possibly be demonstrating this host antitumor effect, which may then correlate with OS.

Two prior studies [33, 34]—have specifically investigated the association between inflammatory markers and OS in patients with BM, albeit without assessing simultaneous corticosteroid use. Shaverdian et al. [33] demonstrated that pre-treatment markers, including platelet count and albumin count, were associated with OS in 70 patients with BM, but not the NLR. Importantly, the authors did not report on systemic therapy use, an important factor in assessing OS. In addition, they only included BM due to breast, melanoma or non-small cell lung cancer (NSCLC). Mitsuya et al. [34] focused on resected BM: in a cohort of 105 patients, they found that $\text{NLR} < 5$ was associated with improved OS. Systemic therapy use, however, was significantly higher in the cohort with $\text{NLR} < 5$: 55 vs. 17%. Our findings add to these earlier works by investigating the role of NLR in a large population of BM from various histologies (NSCLC, melanoma, breast, renal cell carcinoma, others) with similar rates of systemic therapy use. Moreover, we found no difference in corticosteroid use between the two cohorts, which can cause a leftward shift and subsequent increase in the NLR.

Limitations of this study include its retrospective design and related potential for selection bias due to the non-randomized treatment cohort. In addition, although NLR has been shown to be prognostic in various malignancies, it is ultimately a nonspecific marker that may be a surrogate for global inflammatory state rather than specific for CNS disease. High NLR can also reflect both neutrophilia related to the inflammatory response caused by cancer or other disease states, corticosteroid usage, and the lymphopenia that results from cachexia or cortisol-induced stress response. To account for these shortcomings, we analyzed active systemic disease as well as corticosteroid usage amongst the cohorts and found no differences. In addition, none of the patients in this study had an active infection at time of lab draws. Other strengths of this study include its relatively large patient numbers, homogenous patient treatment methods, capturing details of systemic therapy, including targeted therapy and immunotherapy, follow-up/surveillance schedule, and use of MVA to adjust for potential confounding variables.

Conclusion

Overall, a post-treatment NLR is associated with OS; specifically on MVA, a $\text{NLR} > 6$ (HR: 1.53; 95% CI 1.03–2.26, $p = 0.036$) predicted for an increased risk of death. If prospectively validated, NLR is a simple, systemic marker that can be easily used in clinical settings to determine if more aggressive subsequent management is needed following initial treatment.

Acknowledgements

Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and National Institute of Health/National Cancer Institute under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Nayak L, Lee EQ, Wen PY (2012) Epidemiology of brain metastases. *Curr Oncol Rep* 14(1):48–54 [PubMed: 22012633]
2. Patel KR, Lawson DH, Kudchadkar RR et al. (2015) Two heads better than one? Ipilimumab immunotherapy and radiation therapy for melanoma brain metastases. *Neuro-oncology* 17(10): 1312–1321 [PubMed: 26014049]
3. Chowdhary M, Patel KR, Danish HH, Lawson DH, Khan MK (2016) BRAF inhibitors and radiotherapy for melanoma brain metastases: potential advantages and disadvantages of combination therapy. *OncoTargets Ther* 9:7149–7159
4. Kocher M, Soffiotti R, Abacioglu U et al. (2011) Adjuvant whole brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952–26001 study. *J Clin Oncol* 29(2):134–141 [PubMed: 21041710]
5. Gaspar L, Scott C, Rotman M et al. (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 37(4):745–751 [PubMed: 9128946]
6. Sperduto CM, Watanabe Y, Mullan J et al. (2008) A validation study of a new prognostic index for patients with brain metastases: the Graded Prognostic Assessment. *J Neurosurg* 109(Suppl):87–89 [PubMed: 19123893]
7. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W (2008) A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 70(2):510–514 [PubMed: 17931798]
8. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* 100(1):57–70 [PubMed: 10647931]
9. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144(5):646–674 [PubMed: 21376230]
10. Alagappan M, Pollom EL, von Eyben R et al. (2018) Albumin and neutrophil-lymphocyte ratio (NLR) predict survival in patients with pancreatic adenocarcinoma treated with SBRT. *Am J Clin Oncol* 41(3):242–247 [PubMed: 26757436]
11. Hyder J, Boggs DH, Hanna A, Suntharalingam M, Chuong MD (2016) Changes in neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios during chemoradiation predict for survival and pathologic complete response in trimodality esophageal cancer patients. *J Gastrointest Oncol* 7(2): 189–195 [PubMed: 27034785]
12. Shaverdian N, Veruttipong D, Wang J, Schae D, Kupelian P, Lee P (2016) 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 [PubMed: 26372098]
13. Louveau A, Smirnov I, Keyes TJ et al. (2015) Structural and functional features of central nervous system lymphatic vessels. *Nature* 523(7560):337–341 [PubMed: 26030524]
14. Bambury RM, Teo MY, Power DG et al. (2013) The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. *J Neurooncol* 114(1):149–154 [PubMed: 23780645]
15. Mason M, Maurice C, McNamara MG et al. (2017) Neutrophil-lymphocyte ratio dynamics during concurrent chemo-radiotherapy for glioblastoma is an independent predictor for overall survival. *J Neurooncol* 132(3):463–471 [PubMed: 28332000]
16. Patel KR, Prabhu RS, Kandula S et al. (2014) Intracranial control and radiographic changes with adjuvant radiation therapy for resected brain metastases: whole brain radiotherapy versus stereotactic radiosurgery alone. *J Neurooncol* 120(3):657–663 [PubMed: 25189789]

17. Eaton BR, LaRiviere MJ, Kim S et al. (2015) Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases. *J Neurooncol* 123(1): 103–111 [PubMed: 25862006]
18. Shaw E, Scott C, Souhami L et al. (2000) Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. *Int J Radiat Oncol Biol Phys* 47(2):291–298 [PubMed: 10802351]
19. Patel KR, Chowdhary M, Switchenko JM et al. (2016) BRAF inhibitor and stereotactic radiosurgery is associated with an increased risk of radiation necrosis. *Melanoma Res* 26(4):387–394 [PubMed: 27223498]
20. Keizman D, Ish-Shalom M, Huang P et al. (2012) The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. *Eur J Cancer* 48(2):202–208 [PubMed: 22018713]
21. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 94(446):496–509
22. de Jager CP, Wever PC, Gemen EF et al. (2012) The neutrophil lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS ONE* 7(10):e46561 [PubMed: 23049706]
23. Petrie HT, Klassen LW, Kay HD (1985) Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. *J Immunol* 134(1):230–234 [PubMed: 3871101]
24. el-Hag A, Clark RA (1987) Immunosuppression by activated human neutrophils. Dependence on the myeloperoxidase system. *J Immunol* 139(7):2406–2413 [PubMed: 2821114]
25. McCourt M, Wang JH, Sookhai S, Redmond HP (1999) Proinflammatory mediators stimulate neutrophil-directed angiogenesis. *Arch Surg* 134(12):1325–1331 [PubMed: 10593330]
26. McCourt M, Wang JH, Sookhai S, Redmond HP (2001) Activated human neutrophils release hepatocyte growth factor/scatter factor. *Eur J Surg Oncol* 27(4):396–403 [PubMed: 11417987]
27. Jabło ska E, Kiluk M, Markiewicz W, Piotrowski L, Grabowska Z, Jabło ski J (2001) TNF-alpha, IL-6 and their soluble receptor serum levels and secretion by neutrophils in cancer patients. *Arch Immunol Ther Exp* 49(1):63–69
28. Shamamian P, Schwartz JD, Pocock BJ et al. (2001) Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: a role for inflammatory cells in tumor invasion and angiogenesis. *J Cell Physiol* 189(2):197–206 [PubMed: 11598905]
29. Scapini P, Nesi L, Morini M et al. (2002) Generation of biologically active angiostatin kringle 1–3 by activated human neutrophils. *J Immunol* 168(11):5798–5804 [PubMed: 12023382]
30. Kitayama J, Yasuda K, Kawai K, Sunami E, Nagawa H (2010) Circulating lymphocyte is in an important determinant of the effectiveness of preoperative radiotherapy in advaced rectal cancer. *Radiat Oncol* 5:47 [PubMed: 20525293]
31. Sharabi AB, Nirschl CJ, Kochel CM et al. (2015) Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res* 3(4):345–355 [PubMed: 25527358]
32. Dovedi SJ, Adlard AL, Lipowska-Bhalla G et al. (2014) Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* 74(19):5458–5468 [PubMed: 25274032]
33. Shaverdian N, Wang J, Levin-Epstein R et al. (2016) Pro-inflammatory state portends poor outcomes with stereotactic radiosurgery for brain metastases. *Anticancer Res* 36(10):5333–5337 [PubMed: 27798896]
34. Mitsuya K, Nakasu Y, Kurakane T, Hayashi N, Harada H, Nozaki K (2017) Elevated preoperative neutrophil-to-lymphocyte ratio as a predictor of worse survival after resection in patients with brain metastasis. *J Neurosurg* 127(2):433–437 [PubMed: 27911233]

Post-RT NLR	No. of Subject	Event	Censored	Median Survival (95% CI)	6 Mo Survival	12 Mo Survival	18 Mo Survival	24 Mo Survival	30 Mo Survival
≤6	137	101 (74%)	36 (26%)	20.7 (17.4, 25.5)	94.8% (89.5%, 97.5%)	72.9% (64.4%, 79.6%)	55.4% (46.4%, 63.5%)	43.8% (34.9%, 52.4%)	35.5% (26.9%, 44.1%)
>6	51	38 (75%)	13 (25%)	14.7 (10, 16.8)	90.1% (77.8%, 95.8%)	59.9% (44.5%, 72.3%)	32.8% (19.7%, 46.5%)	24.6% (12.9%, 38.3%)	19.1% (8.8%, 32.4%)

Fig. 1.
Kaplan-Meier model comparing survival for patients with BM and post-treatment (i.e. radiosurgery) neutrophil-to-lymphocyte ratio ≤6 versus >6

Table 1

Baseline patient and lesion-level characteristics between neutrophil-to-lymphocyte ratio (NLR) > 6 versus 6

Variable	Level	NLR ≤ 6 N = 137 patients or 233 BM	NLR > 6 N = 51 patients or 95 BM	p Value
Sex	Male	69 (50.4%)	22 (43.1%)	0.378
	Female	68 (49.6%)	29 (56.9%)	
Age	≤ 65	102 (74.5%)	37 (72.5%)	0.792
	> 65	35 (25.5%)	14 (27.5%)	
Primary histology	NSCLC	48 (35.0%)	25 (49.0%)	0.395
	Breast	25 (18.2%)	8 (15.7%)	
	Melanoma	44 (32.1%)	10 (19.6%)	
	RCC	8 (5.8%)	3 (5.9%)	
	Other	12 (8.8%)	5 (9.8%)	
ECOG performance status	0	61 (44.5%)	17 (33.3%)	0.026
	1	62 (45.3%)	21 (41.2%)	
	2–3	14 (10.2%)	13 (25.5%)	
Active systemic disease	Yes	74 (54.0%)	24 (47.1%)	0.396
	No	63 (46.0%)	27 (52.9%)	
Extracranial metastases	Yes	63 (46.0%)	22 (43.1%)	0.727
	No	74 (54.0%)	29 (56.9%)	
Grade prognostic assessment	0–1.0	9 (6.6%)	5 (9.8%)	0.837
	1.5–2.5	83 (60.6%)	31 (60.8%)	
	3.0	24 (17.5%)	9 (17.6%)	
	3.5–4.0	21 (15.3%)	6 (11.8%)	
Total number of BM	1	84 (61.3%)	28 (54.9%)	0.426
	> 1	53 (38.7%)	23 (45.1%)	
Number of fractions	1	119 (89.5%)	43 (87.8%)	0.742
	> 1	14 (10.5%)	6 (12.2%)	
Concurrent steroid use	Yes	34 (24.8%)	14 (27.5%)	0.652
	No	103 (75.2%)	37 (72.5%)	
Any systemic therapy	Yes	126 (92.0%)	46 (90.2%)	0.698
	No	11 (8.0%)	5 (9.8%)	
Systemic therapy prior to SRS	Yes	88 (64.2%)	31 (60.8%)	0.663
	No	49 (35.8%)	20 (39.2%)	
Chemotherapy prior to SRS	Yes	70 (51.1%)	25 (49.0%)	0.800
	No	67 (48.9%)	26 (51.0%)	
Targeted therapy prior to SRS	Yes	25 (18.2%)	6 (11.8%)	0.287
	No	112 (81.8%)	45 (88.2%)	
Immunotherapy prior to SRS	Yes	17 (12.4%)	6 (11.8%)	0.905
	No	120 (87.6%)	45 (88.2%)	
Systemic therapy post SRS	Yes	116 (84.7%)	41 (80.4%)	0.482
	No	21 (15.3%)	10 (19.6%)	
Chemotherapy post SRS	Yes	88 (64.2%)	37 (72.5%)	0.283

Variable	Level	NLR ≤ 6 N = 137 patients or 233 BM	NLR > 6 N = 51 patients or 95 BM	p Value
Targeted therapy post SRS	No	49 (35.8%)	14 (27.5%)	0.526
	Yes	47 (34.3%)	15 (29.4%)	
Immunotherapy post SRS	No	90 (65.7%)	36 (70.6%)	0.535
	Yes	18 (13.1%)	5 (9.8%)	
Resection of BM	No	119 (86.9%)	46 (90.2%)	0.455
	Yes	53 (22.9%)	22 (23.2%)	
	No	166 (71.9%)	71 (74.7%)	
BM laterality	Prior resection to different lesion	12 (5.2%)	2 (2.1%)	0.239
	Right	111 (48.7%)	39 (41.5%)	
	Left	117 (51.3%)	55 (58.5%)	
BM location	Frontal	83 (35.6%)	31 (32.6%)	0.987
	Parietal	48 (20.6%)	23 (24.2%)	
	Temporal	27 (11.6%)	10 (10.5%)	
	Occipital	19 (8.2%)	7 (7.4%)	
	Cerebellum	51 (21.9%)	22 (23.2%)	
	Brainstem	2 (0.9%)	1 (1.1%)	
	Other	3 (1.3%)	1 (1.1%)	
Framed SRS	Framed	210 (90.1%)	86 (90.5%)	0.912
	Frameless	23 (9.9%)	9 (9.5%)	
Number of fractions	Mean	1.24	1.24	0.957
	Median	1	1	
SRS total dose	Mean	19.9	19.8	0.854
	Median	20	20	
SRS dose/fraction	Mean	18.49	18.13	0.453
	Median	20	20	
Prescription IDL	Mean	59.95	60.34	0.927
	Median	80	80	
Conformality index	Mean	1.7	1.73	0.473
	Median	1.63	1.59	
GTV (cc)	Mean	7.23	7.48	0.621
	Median	2.66	3.34	
PTV (cc)	Mean	11.21	13.74	0.758
	Median	6.04	6.78	

Bold value indicates statistical significance, $p < 0.05$

BM brain metastases, *NSCLC* non small cell lung cancer, *RCC* renal cell carcinoma, *ECOG* Eastern Cooperative Oncology Group, *SRS* stereotactic radiosurgery, *IDL* isodose line, *GTV* gross tumor volume, *PTV* planning target volume

Table 2

Univariate analysis for overall survival

Variable	Level	Overall survival		
		N	Hazard ratio	Log rank p value
Post-SRS NLR	> 6	51	1.52 (1.04–2.21)	0.028
	6	137	-	
Sex	Female	107	0.93 (0.68–1.29)	0.674
	Male	96	-	
Age	> 65	53	0.87 (0.60–1.27)	0.470
	65	150	-	
Primary histology	NSCLC	77	-	0.136
	Breast	38	1.03 (0.65–1.63)	
	Melanoma	56	0.99 (0.66–1.47)	
	RCC	14	1.17 (0.61–2.23)	
	Other	18	2.09 (1.15–3.78)	
ECOG performance status	0	84	-	0.542
	1	90	1.08 (0.76–1.53)	
	2–3	29	1.32 (0.81–2.17)	
Active systemic disease	Yes	105	1.26 (0.91–1.74)	0.160
	No	98	-	
Extracranial metastases	Yes	92	1.93 (1.38–2.69)	< 0.001
	No	111	-	
Grade prognostic assessment	0–1.0	14	-	0.036
	1.5–2.5	122	0.68 (0.38–1.22)	
	3.0	38	0.44 (0.23–0.86)	
	3.5–4.0	29	0.46 (0.23–0.93)	
Total number of BM	1	122	-	0.477
	> 1	81	1.13 (0.81–1.57)	
Number of fractions	1	173	-	0.497
	> 1	24	0.82 (0.46–1.45)	
Any systemic therapy	Yes	183	0.89 (0.51–1.54)	0.665
	No	20	-	
Systemic therapy prior to SRS	Yes	125	1.15 (0.82–1.60)	0.423
	No	78	-	
Chemotherapy prior to SRS	Yes	101	1.13 (0.82–1.56)	0.449
	No	102	-	
Targeted therapy prior to SRS	Yes	32	0.76 (0.49–1.20)	0.245
	No	171	-	
Immunotherapy prior to SRS	Yes	23	0.76 (0.49–1.20)	0.790
	No	180	-	
Systemic therapy post SRS	Yes	167	0.98 (0.64–1.51)	0.929
	No	36	-	

Variable	Level	Overall survival		
		N	Hazard ratio	Log rank p value
Chemotherapy post SRS	Yes	133	1.36 (0.96–1.94)	0.083
	No	70	-	
Targeted therapy post SRS	Yes	64	0.80 (0.57–1.13)	0.203
	No	139	-	
Immunotherapy post SRS	Yes	23	0.73 (0.42–1.27)	0.262
	No	180	-	

Bold values indicate statistical significance, $p < 0.05$

SRS stereotactic radiosurgery, *NLR* neutrophil-to-lymphocyte ratio, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma, *ECOG* Eastern Cooperative Oncology Group, *BM* brain metastases

Table 3

Multivariable analysis for overall survival

Covariate	Level	Overall Survival	
		Hazard ratio (HR)	HR p value
Post-SRS NLR	> 6	1.53 (1.03–2.26)	0.036
	6	-	-
Active systemic disease	Yes	0.90 (0.52–1.30)	0.571
	No	-	-
Extracranial metastases	Yes	1.90 (1.30–2.78)	< 0.001
	No	-	-
Graded prognostic assessment	3.5–4.0	0.74 (0.33–1.66)	0.466
	3.0	0.67 (0.21–1.39)	0.283
	1.5–2.5	0.85 (0.46–1.60)	0.619
	0.0–1.0	-	-
Targeted therapy post SRS	No	1.21 (0.84–1.76)	0.306
	Yes	-	-
Immunotherapy post SRS	No	1.40 (0.80–2.47)	0.239
	Yes	-	-

Bold values indicate statistical significance, $p < 0.05$ *SRS* stereotactic radiosurgery, *NLR* neutrophil-to-lymphocyte ratio