Elevated preoperative neutrophil-to-lymphocyte ratio as a predictor of worse survival after resection in patients with brain metastasis

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OBJECTIVE The median postoperative survival duration of patients with brain metastases who undergo tumor resection is 12 months. Most of these patients die of systemic metastases or the progression of primary cancer but not brain metastases. The criteria for indicating resection are still controversial. Systemic assessment is restricted, especially in patients who need emergent management for their large-size or life-threatening brain metastases. The neutrophil-to-lymphocyte ratio (NLR) is reported to correlate with survival time or progression-free survival in patients with various cancers. However, NLR has not been assessed in patients with brain metastases. The impact of NLR on the survival data of patients who had undergone resection of brain metastases was retrospectively analyzed.

METHODS The clinical records of patients who underwent resection of brain metastases at Shizuoka Cancer Center between May 2007 and January 2015 were retrospectively analyzed. NLR was calculated by using the data obtained from the latest examination before resection and before the administration of steroid therapy. Kaplan-Meier curves were used for the assessment of overall survival (OS).

RESULTS Of the 105 patients included, 67 patients were male. The median age of the patients was 63 years (range 36–90 years). The primary cancers were lung, colon, breast, uterus, and other cancers in 48, 19, 10, 8, and 20 patients, respectively. The postresection median survival duration was 12 months (range 1–91 months) for the entire series. The optimum NLR threshold value was identified as 5. A significant difference in the median OS was found: 14 months for 82 patients with an NLR < 5 versus 5 months for 23 patients with an NLR ≥ 5 ($p = 0.001$).

CONCLUSIONS In this study, an elevated preoperative NLR is a predictor of worse survival after resection for brain metastases. NLR is a simple, systemic marker and can be used in clinical settings for decision making regarding resection in patients with brain metastases.

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KEY WORDS metastatic brain tumor; neutrophil-to-lymphocyte ratio; prognostic factor; surgery; oncology

BRAIN metastases occur in 10% to 40% of patients with cancer and are the most common central nervous system neoplasm in adults.^{28,33} With increased surveillance, improved control of systemic cancer, and prolonged survival, the incidence of patients with brain metastases is increasing.¹⁷ The management of brain metastases has been revolutionized in clinical oncology by 4 developments: improved brain imaging, improved management of systemic diseases, the distribution of stereo-

tactic irradiation, and the extension of less invasive surgical techniques that enable brain metastases to be removed even from eloquent brain areas with minimal morbidity.⁵ Although stereotactic irradiation and pharmacotherapies contribute to the treatment outcome of patients with brain metastasis, resection is still a mainstay for large brain metastases.

The indications for resection include a symptomatic mass, a mass with considerable edema requiring high-dose

ABBREVIATIONS DS-GPA = diagnosis-specific graded prognostic assessment; KPS = Karnofsky Performance Status; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; RPA = recursive partitioning analysis.

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steroids, a mass greater than 3 cm, and a mass with an unknown primary cancer.⁵ In addition, an estimated life expectancy of more than 3 or 6 months is a factor used to indicate a candidate for resection. Patients in the terminal stage may receive neither a survival benefit nor an improvement in their quality of life from invasive treatments.

Several studies have attempted to identify prognostic factors and predict the life expectancy of patients with brain metastases, and classification systems including recursive partitioning analysis (RPA) classification and diagnosis-specific graded prognostic assessment (DS-GPA) have been developed.^{9,29} These classification systems have been mainly validated in patient populations treated with radiotherapy.^{1,6,10} A simple and reliable marker that reflects the systemic conditions of patients with brain metastases is needed in the decision-making process for resection.^{21,23,26,31}

Interest in the host inflammatory response to neoplasms is increasing. Inflammatory cells accumulating around cancer cells play an important role in the prognosis of patients. Patients with lymphocyte infiltration around the tumor may have a better prognosis than those without infiltration, and patients with neutrophils infiltrating around their cancers may be associated with a poor prognosis.^{15,35} A systematic inflammatory response leads to changes in the relative levels of circulating white blood cells, resulting in an increase in neutrophils and a decrease in lymphocytes with the progression of cancer.²⁵ Recently, an association was reported between a high neutrophil-to-lymphocyte ratio (NLR) and shorter survival time in patients with various cancers,^{4,8,11,13,14,16,19,22,27,34} including glioblastoma.^{3,12,18} However, the value of preoperative NLR in the assessment of candidates for resection for brain metastasis has not been evaluated.

The aim of this study was to retrospectively evaluate outcomes and prognostic factors, including NLR, in patients with brain metastases who underwent resection. We hypothesized that preoperative NLR contributes to identifying patients likely to benefit from resection.

Methods

Patient Population

We retrospectively studied patients who underwent resection as their first surgery for brain metastases with complete laboratory data available at Shizuoka Cancer Center between May 2007 and January 2015. All patients were diagnosed with brain metastases using MRI and had a histologically proven metastatic tumor in the brain. No patient underwent pre- and postoperative immunotherapy.

The patients' clinical data included their age, sex, primary cancer, and Karnofsky Performance Status (KPS). Data from routine laboratory measurements were recorded to determine complete blood counts with differential leukocyte counts. Blood sampling was performed 1 to 14 days before surgery and under conditions without steroid therapy. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The RPA class and DS-GPA score of each patient were estimated using published criteria.⁹ The institutional review board approved the analysis in this study.

Treatment

Our cancer board approved resection for patients with the following characteristics: 1) a postsurgery life expectancy of 6 months or longer based on information from medical oncologists; 2) single metastases measuring more than 3 cm, or multiple or smaller tumors associated with serious symptoms that were expected to improve with resection; and 3) no clinical manifestations or radiological findings indicating leptomeningeal metastasis. Resection with a safety margin or enucleation was applied as neurosurgical techniques depending on the eloquence and border zone pathology.²⁰ In principle, adjuvant radiotherapy usually began 1 to 2 weeks after surgery. Adjuvant stereotactic radiotherapy was used only for patients with a surgical remnant or unresected lesions. After brain metastases were controlled, the patients received further systemic therapy or best supportive care according to decisions made by the medical oncologists. In patients who had tumor recurrence after radiotherapy, the indication for salvage treatment was judged via discussion at our cancer board with senior radiation oncologists. Nineteen patients (18%) underwent salvage resection after radiotherapy.

Statistical Analyses

Overall survival (OS) time was calculated from the date of the first resection for brain metastases to the date of death due to any cause. The statistical analysis was performed using JMP (version 11; SAS Institute). The data for survival time were analyzed using the Kaplan-Meier method. Values were compared using the log-rank test. Frequency analysis was performed using the Fisher exact test. A *p* value < 0.05 was considered statistically significant.

Results

The characteristics of all patients are shown in Table 1. Sixty-three patients were male, and the median age of the patients was 63 years (range 36–90 years). The primary cancers were lung, colon, breast, uterus, stomach, esophagus, kidney, thyroid, ovary, and other cancers in 48, 19, 10, 8, 4, 3, 3, 2, 2, and 6 patients, respectively. Other cancers included pharyngeal, mandibular, cholangic, vaginal, and bladder cancer and leiomyosarcoma. After surgery, adjuvant radiation therapy was administered. Thirteen patients received local radiation therapy or stereotactic irradiation, and 72 patients received whole-brain RT. Table 2 reports the adjuvant radiotherapy and systemic chemotherapy administered to our cohort. Patients with an NLR < 5 underwent chemotherapy significantly more frequently than patients with an NLR ≥ 5. The median survival time of all the cohorts was 12 months (range 1–91 months). The median NLR prior to surgery was 2.91 (mean 4.19; range 1.0–20.0; 95% CI 3.5–4.86). The receiver operating characteristic curve showed a cutoff value of 5.0 as a marker of more than 6 months of survival with a sensitivity of 87.0% and specificity of 46.4%. The area under the curve was 0.704 (Fig. 1). We set the optimum NLR threshold value as 5, as in previous reports of other cancers.³⁴ Of 105 patients, 82 (78%) patients had an NLR of < 5. The median OS after resection in the patients with an NLR of < 5 was 14 months,

TABLE 1. Patient characteristics and NLR

Variable	No. of Patients (%)		
	All Patients	NLR < 5	NLR ≥ 5
No. of patients	105	82	23
Sex			
Male	67 (64)	48 (59)	19 (83)
Female	38 (36)	34 (41)	4 (17)
Age in yrs			
<65	58 (55)	43 (52)	15 (65)
≥65	47 (45)	39 (48)	8 (35)
KPS			
90–100	9 (9)	7 (9)	2 (8)
70–80	37 (35)	32 (39)	5 (22)
50–60	49 (46)	38 (46)	11 (48)
40	10 (10)	5 (6)	5 (22)
Primary cancer			
Lung	48	37	11
Colon	19	15	4
Breast	10	10	0
Uterus*	8*	6	2
Stomach	4	3	1
Esophagus	3	2	1
Kidney	3	3	0
Thyroid*	2*	1	1
Ovary*	2*	2	0
Other*	6*	3	3
RPA classification			
Class 1	9 (9)	8 (10)	1 (4)
Class 2	37 (35)	31 (38)	6 (26)
Class 3	59 (56)	43 (52)	16 (70)

* Patients with brain metastases from cancers not listed in DS-GPA.

and the median OS of those with an NLR of ≥ 5 was 5 months ($p = 0.01$ according to the log-rank test; Fig. 2).

Discussion

Brain metastases are no longer considered a single entity but a special site of metastatic cancer; they are assessed

TABLE 2. Postoperative treatment and NLR

Variable	All Patients	NLR < 5	NLR ≥ 5
No. of patients	105	82	23
Radiotherapy after surgery (%)			
Whole brain	72 (69)	56 (68)	16 (70)
Local	13 (12)	10 (12)	3 (13)
None	20 (19)	16 (20)	4 (17)
Systemic therapy after surgery (%)			
Chemotherapy	49 (47)	45 (55)	4 (17)
No chemotherapy	40 (38)	24 (29)	16 (70)
Not needed (no extracranial metastasis)	16 (15)	13 (16)	3 (13)

FIG. 1. Receiver operating characteristic curve showing an area under the curve of 0.704.

and managed in the context of the primary cancer and the patient's overall systemic options. Treatment is multidisciplinary and individualized. Resection is important in the management of patients with brain metastases. Patients with obstructive hydrocephalus, large or cystic tumors, tumors with mass effect or marked edema, or neurological deficits despite steroid therapy are best treated with craniotomy and resection of the brain metastases.⁵

The decision to perform resection in each patient must be made urgently but cautiously because surgery has a potential concern for morbidity and mortality. The selection criteria should include both the patient's whole systemic condition and the characteristics of the brain metastases. Despite successful resection, a certain number of patients

FIG. 2. Kaplan-Meier survival curves for the patients with a high preoperative NLR (≥ 5) in comparison with those patients with a low preoperative NLR (< 5). The median OS of the patients with a high NLR is 5 months, whereas that of the patients with a low NLR is 14 months.

die within a short postoperative period as a result of rapid systemic tumor progression or an impaired general condition.² The survival of patients with advanced cancer is linked to a complex interplay of disease progression, performance status, inflammatory status, cachexia, and other factors.³⁰

NLR is simple and easy to calculate using routine laboratory data without an additional technique or cost. The results of this study indicated that elevated NLR was a clear clinical predictor of poor outcome in patients who underwent resection for brain metastases. Consistent with previous studies of advanced cancers, elevated NLR was a strong prognostic factor.^{4,8,11,13,14,16,19,22,27,34}

The role of the host inflammatory response in determining tumor spread is increasingly recognized. The association between elevated NLR and poor prognosis has several possible explanations. An elevated NLR may be a consequence of more neutrophils, fewer lymphocytes, or both. Cancers are known to release myeloid growth factors, and this subsequently leads to the increased production of neutrophils.³² Meanwhile, circulating neutrophils have been shown to contain and secrete vascular endothelial growth factor, tumor necrosis factor, and other cytokines that contribute to cancer progression. Therefore, an elevated neutrophil count stimulates tumor angiogenesis and aids in the proliferation of neoplasms. This vicious cycle may lead to the poor outcome of affected patients.³⁰ Another possible explanation is that patients with an elevated NLR have lymphocytopenia and decreased lymphocyte function. An increased level of neutrophils suppresses the cytolytic activity of lymphocytes, natural killer cells, and activated T cells.^{7,24}

Since the Radiation Therapy Oncology Group performed an RPA for the prediction of survival in the late 1990s, several assessment systems have provided information on individual prognosis. The RPA classification is a simple method for predicting outcome based on KPS, age, primary tumor control, and extracranial metastasis.⁹ RPA can be applied to any kind of primary cancer. RPA sometimes cannot separate Class 2 cases from Class 3 cases with the same low KPS by their neurological deficits, especially in patients with large brain metastases. Our study showed that the Kaplan-Meier curves of the RPA Class 2 and Class 3 patients were nearly identical, as previously reported.³¹ DS-GPA is a refined new system for the prediction of survival time in patients with brain metastases from lung cancer, breast cancer, melanoma, gastrointestinal tract cancers, and renal cell carcinoma. However, DS-GPA cannot be applied to patients with brain metastases from cancers not listed in DS-GPA, which are not rare and accounted for 17% of the patients in our study (Table 1). DS-GPA also has the same problem as RPA classification in the estimation of lower KPS. Therefore, we recommend including NLR in the systemic assessment process for resection candidates.

There are 3 limitations of this study. 1) Neutrophilia is sometimes nonspecific, and the sensitivity is good but the specificity is moderately low. When subclinical infection occurs, neutrophils are often dominant. 2) During corticosteroid treatment, neutrophilia is occasionally observed, and we excluded data during corticosteroid prescription. 3) Acute stress could increase the number of neutrophils.

Conclusions

In our study, elevated preoperative NLR is a predictor of worse survival after resection for brain metastases. Further research will be needed to understand the interaction of brain metastases and immunological environments. The future refinement of the prognostic markers of brain metastases will identify a population of patients likely to benefit from surgical intervention.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Mitsuya. Acquisition of data: Mitsuya, Kurakane. Analysis and interpretation of data: all authors. Drafting the article: Mitsuya. Critically revising the article: Mitsuya, Nakasu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mitsuya. Statistical analysis: Mitsuya, Kurakane. Administrative/technical/material support: Nakasu. Study supervision: Nakasu, Nozaki.

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