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Neutrophil–to–Lymphocyte Ratio Predicts Survival After Whole-brain Radiotherapy in Non-small Cell Lung Cancer

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Abstract. *Aim: This study aimed to identify prognostic factors for response to whole-brain radiotherapy (WBRT) in patients with brain metastases (BMs) from non-small cell lung cancer (NSCLC). Patients and Methods: This study retrospectively evaluated 100 patients who underwent WBRT for BMs from NSCLC between December 2012 and October 2017. Clinical factors were tested for associations with overall survival after WBRT. Results: The median follow-up time was 134 days (range=14-1,395 days), the median survival time was 143 days, and the 1-year survival rate was 30.4%. Univariate and multivariate analyses revealed that better survival was independently associated with expression of programmed death-ligand 1 (PD-L1), no previous treatment for BMs, no extracranial disease, and a neutrophil–to–lymphocyte ratio (NLR) of <5.0. Conclusion: A low NLR and positive PD-L1 expression independently predict better prognosis in patients with BMs from NSCLC after WBRT. These findings suggest that the potential immune response may influence survival among patients with BMs.*

The lung is the most common primary site for brain metastases (BMs), which affect up to 30% of patients with lung cancer (1). There are several models for predicting the prognosis of patients with BMs, such as the Radiation Therapy Oncology Group–Recursive Partitioning Analysis (RTOG-RPA) and the Graded Prognostic Assessment (GPA) (2, 3). In addition, a recent report has indicated that gene mutation status can help predict outcomes after radiosurgery for patients with multiple BMs (4). However, patients who are candidates for whole-brain radiotherapy (WBRT) are thought to have unfavorable prognoses, despite the absence of clear prognostic factors. In this context, WBRT is a standard palliative treatment for patients with BMs who are unsuitable for surgical resection or stereotactic radiosurgery/radiotherapy (SRS/SRT) (5), although it reportedly provides a limited clinical benefit (6). Therefore, it can be difficult to use the RPA or GPA prognostic models for patients who are undergoing WBRT, as these models incorporate extracranial metastasis status and number of BMs.

Immune checkpoint inhibitors have significantly improved survival outcomes among patients with recurrent and refractory non-small cell lung cancer (NSCLC) (7, 8). In addition, pre-clinical and clinical studies have indicated that immunotherapy and radiotherapy have synergistic effects, with a high possibility of abscopal effects, which may significantly alter the current treatment strategies for metastatic diseases (9). Furthermore, Shaverdian *et al.* recently reported that previous radiotherapy may prolong overall survival among patients who are receiving programmed death-1 (PD-1) blockade for advanced NSCLC covered with patients who had not previously undergone radiotherapy (10). Thus, WBRT might be useful for both intracranial tumor control and improving the immune response to systemic disease. However, there are no clear prognostic factors for WBRT, especially among patients with BMs. Therefore, the present study aimed to identify prognostic factors for response to radiotherapy among patients with BMs from NSCLC, especially in terms of their potential immune response.

Patients and Methods

Patients. This retrospective study was approved by our Institutional Review Board (reference number 30-028), and all patients had provided informed consent for WBRT. Between December 2012 and October 2017, consecutive patients with BMs who underwent WBRT at our Institution were identified. Two patients who had follow-up durations of less than 6 months without any specific events were excluded. All patients had pathologically confirmed NSCLC and a diagnosis of BMs based on computed tomography or magnetic resonance imaging findings. Blood test data from between

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4 weeks before WBRT and the first day of the WBRT course were available for all but three patients, with one patient having completed the testing on the second day of the WBRT course, another patient having completed the testing 3 months before the WBRT, and the last patient having serum lactate dehydrogenase (LDH) data that were acquired 2 months before WBRT. These patients were all included in the present study because there were no clinical findings that might have affected results.

All patients were treated using conventional external beam radiotherapy with a typical photon energy of 4-6 MV and opposed lateral treatment fields that encompassed the entire brain. The prescribed dose was calculated at the isocenter of the radiation fields based on daily treatments. Two of the included patients received a dose of 30 Gy in 12 fractions followed by 15 Gy in six fractions for the gross tumor volume (total of 45 Gy in 18 fractions), and one patient received a dose of 35 Gy in 14 fractions followed by 5 Gy in two fractions for the gross tumor volume (total of40 Gy in 16 fractions). No patients underwent planned WBRT combined with SRS/SRT.

Statistical analysis. Data are reported as median (range) or number (percentage). Time-to-event analyses were performed from the start of radiotherapy to the emergence of the event. The Kaplan–Meier method and log-rank test were used to compare the curves for cumulative intracranial disease control and overall survival. Potential prognostic factors were evaluated using the Cox proportional hazards model, and the results are reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Factors with *p*-values of less than 0.2 in the univariate analyses were included in the multivariate model. All analyses were performed using JMP software (version 12.2.0; SAS Institute, Cary, NC, USA), and differences were considered statistically significant at *p*-values of less than 0.05.

Results

The patients' characteristics are shown in Table I. The median follow-up time was 134 days (range=14-1,423 days). The survival curves are shown in Figure 1. Among the 66 patients (66%) with symptomatic BMs, 39 (59%) experienced symptom improvement after WBRT. Eighty-seven patients (87%) died during the follow-up (Table I). Six out of seven patients with programmed death-ligand 1 (PD-L1) overexpression received anti-PD-1 therapy. No grade 3 or greater toxicities were observed.

The results of the univariate and multivariate analyses are shown in Table II. Univariate analyses revealed that better survival was associated with an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0-1, adenocarcinoma pathology, PD-L1 expression, no history of local therapy for BMs, no extracranial disease, LDH level of <1.5 times the upper limit of normal, a neutrophil–to–lymphocyte ratio (NLR) of less than 5.0 (11-13), an RPA class of 2 or less, and a GPA score of 1.5 or more. In the multivariate analyses, better survival was independently associated with PD-L1 expression, no history of local therapy for BMs, no extracranial disease, and an NLR of less than 5.0 (Figure 2).

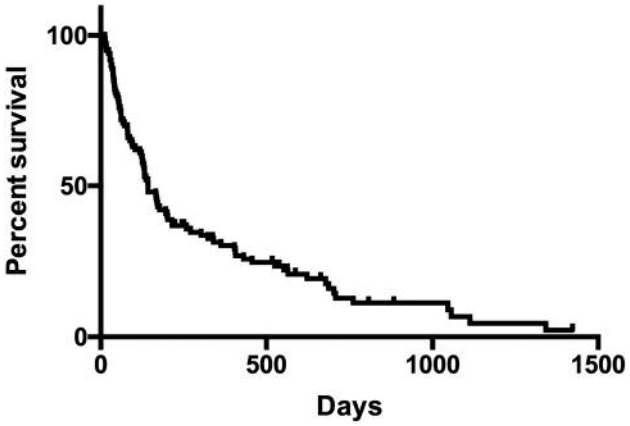

Figure 1. *Overall survival after whole-brain radiotherapy. The median survival interval was 143 days, and the 1-year survival rate was 30.4%.*

Discussion

There are various applications for using WBRT to treat BMs, such as with/without surgical resection or radiosurgery, or as palliative treatment for patients with a poor prognosis. Immune checkpoint inhibitors have also been dramatically changing the modern treatment options for metastases, with a clear survival benefit among patients with metastatic NSCLC (7, 8). Moreover, local radiotherapy reportedly improves the immune response to metastatic tumors (9). Thus, radiotherapy can help improve palliative care and also enhance the immune response to systemic disease in combination with immune therapy. The recent KEYNOTE-001 trial also revealed favorable outcomes among patients who had previously received radiotherapy (10). Although there is a lack of prognostic data for predicting the potential immune response among patients who receive WBRT for NSCLC, our finding may help support a shift in the current paradigm of immune therapy and radiotherapy.

Activated T-cells can be suppressed by marked neutrophil infiltration, and a high NLR may reduce the effects of the lymphocyte-mediated cellular immune response, which could promote cancer progression (11, 14). In addition, the pretreatment NLR among patients with NSCLC has been prospectively shown to be negatively correlated with prognosis (12). Furthermore, a previous report indicated that the NLR might predict the effects of immune checkpoint inhibitors in patients with NSCLC (13). However, there are limited data regarding the use of NLR to predict the response of patients with NSCLC to WBRT. To the best of our knowledge, this is the first study to indicate that patients with a low NLR may experience prolonged survival after WBRT for advanced NSCLC, which highlights a potential immune-mediated response in

Table I. *Patient clinicopathological characteristics (n=100).*

		Value
Age, years	Median (range)	67 (29-83)
Gender, n (%)	Male	62 (62)
	Female	38 (38)
Smoking, pack-years	Median (range)	20 (0-162)
ECOG-PS, n (%)	0	18 (18)
	1	49 (49)
	2	23 (23)
	3	9 (9)
	4	1 (1)
Pathological type, n (%)	Adenocarcinoma	82 (82)
	Squamous cell carcinoma	12 (12)
	Other	6 (6)
EGFR mutation, n (%)	Positive	46 (46)
	Negative	42 (42)
	Unknown	12 (12)
ALK rearrangement, n (%)	Positive	7 (7)
	Negative	69 (69)
	Unknown	24 (24)
PD-L1 status, n (%)	Positive	7 (7)
	Negative	5 (5)
	Unknown	88 (88)
Anti-PD-1 therapy, n (%)	Yes	22 (22)
	Before WBRT	10 (45)
	After WBRT	12 (55)
	No	78 (78)
Days from diagnosis to first appearance of BMs[†]	Median (range)	175 (0-4,236)
History of local treatment for BMs, n (%)[§]	Yes	24 (100)
	SRS	18 (75)
	Surgery	3 (13)
	SRS and surgery	3 (13)
	No	76
Maximum diameter of BMs, mm	Median (range)	15 (6-55)
Number of BMs, n (%)	1	8 (8)
	2	10 (10)
	3	9 (9)
	4	5 (5)
	5	9 (9)
	≥6	59 (59)
Total prescribed dose in Gy	Median (range)	30 (15-45)
Number of fractions	Median (range)	10 (5-18)
BED10 in Gy	Median (range)	39 (19.5-56.3)
RPA class, n (%)	1	2 (2)
	2	74 (74)
	3	24 (24)
GPA score, n (%)	0	18 (18)
	0.5	22 (22)
	1.0	30 (30)
	1.5	18 (18)
	2.0	8 (8)
	2.5	3 (3)
	3.5	1 (1)

ECOG-PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; *ALK*, anaplastic lymphoma kinase gene; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; BMs, brain metastases; SRS, stereotactic radiosurgery; BED, biologically effective dose; RPA, Radiation Therapy Oncology Group–recursive partitioning analysis; GPA, graded prognostic assessment. [†]BMs at initial diagnosis were considered detected on day 0. [§]Local treatment included SRS and surgical resection.

Table II. *Factors affecting overall survival*.

Factor	Patients (n=100)	1-Year survival (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age						
<65 Years	38	28.5	1			
≥65 Years	62	31.7	1.2377 (0.8035-1.9365)	0.3363		
Gender						
Male	62	31.9	1			
Female	38	29.0	0.9431 (0.6056-1.4495)	0.7914		
ECOG-PS						
0-1	66	36.6	1		1	
≥2	34	18.2	2.4380 (1.5178-3.8573)	0.0003	1.3000 (0.5061-2.9305)	0.5617
Smoking, pack-years						
<30	55	37.3	1		1	
≥30	45	22.0	1.3537 (0.8775-2.0771)	0.1694	1.0667 (0.5975-1.8799)	0.8250
Pathological type						
Adenocarcinoma	82	33.8	1		1	
Non-adenocarcinoma	18	11.1	1.8271 (1.0125-3.1126)	0.0456	1.8319 (0.9398 -3.4146)	0.0743
Clinical stage at initial diagnosis*						
I-III	34	28.9	1			
IV	66	31.2	0.9239 (0.5913-1.4765)	0.7346		
EGFR mutation						
Negative/unknown	54	31.3	1			
Positive	46	29.7	0.8854 (0.5704-1.3666)	0.5829		
ALK rearrangement						
Negative/unknown	93	31.9	1			
Positive	7	0.0	1.2194 (0.4700-2.6053)	0.6526		
PD-L1 status						
Negative/unknown	93	26.3	1		1	0.0008
Positive	7	85.7	0.0928 (0.0053-0.4184)	0.0002	0.0804 (0.0044-0.4145)	
Use of anti-PD-1 therapy						
Yes	22	40.9	1		1	
No	78	27.5	1.6789 (0.9900-3.0295)	0.0547	1.1322 (0.6028-2.2370)	0.7073
Presence of BMs at initial diagnosis						
Yes	40	37.2	1	0.2009		
No	60	25.8	1.3316 (0.8598-2.0913)			
History of local treatment for BMs§						
Yes	24	12.5	1		1	
No	76	36.0	0.4193 (0.2623-0.6911)	0.0009	0.4464 (0.2556-0.7933)	0.0065
Initial diagnosis to first appearance of BMs†						
<175 Days	49	32.4	1			
≥175 Days	51	28.3	1.0123 (0.6570-1.5602)	0.9557		
Symptoms due to BMs						
Yes	66	31.3	1			
No	34	28.5	0.7899 (0.4895-1.2418)	0.3120		
Maximum diameter of BMs						
<3 cm	78	31.5	1			
≥3 cm	22	26.5	1.3726 (0.8160-2.2183)	0.2242		
Number of BMs						
≤3	27	29.6	1			
>3	73	30.6	1.0794 (0.6798-1.7762)	0.7527		
Presence of extracranial diseases						
Yes	94	26.1	1		1	
No	6	100.0	0.1824 (0.0300-0.5814)	0.0015	0.2271 (0.0360-0.7812)	0.0151
Radiotherapeutic dose (BED10)						
<40 Gy	58	27.3	1		1	
≥40 Gy	42	34.6	0.7064 (0.4548-1.0839)	0.1121	1.0947 (0.6568-1.8185)	0.7270

Table II. *Continued*

Table II. *Continued*

Factor	Patients (n=100)	1-Year survival (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
LDH						
<1.5×ULN	75	33.7	1		1	
≥1.5×ULN	25	20.0	1.6595 (1.0106-2.6415)	0.0455	1.6156 (0.9055-2.7995)	0.1025
NLR						
<5.0	58	42.4	1		1	
≥5.0	42	13.9	2.1441 (1.3548-3.3781)	0.0013	2.5560 (1.4420-4.5628)	0.0013
RPA class						
≤2	76	34.6	1		1	
3	24	16.7	2.6366 (1.5795-4.2642)	0.0004	1.7052 (0.6784-4.7117)	0.2629
GPA score						
<1.5	70	25.1	1		1	
≥1.5	30	42.9	0.4443 (0.2649-0.7174)	0.0007	0.5880 (0.3303-1.0233)	0.0604

HR, Hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; *ALK*, anaplastic lymphoma kinase gene; PD-L1, programmed death-ligand 1; PD-1, programmed death-1; BMs, brain metastases; BED, biologically-effective dose; LDH, lactate dehydrogenase; ULN, upper limit of normal; NLR, neutrophil–to–lymphocyte ratio; RPA, Radiation Therapy Oncology Group–recursive partitioning analysis; GPA, graded prognostic assessment. †BMs at the initial diagnosis were considered detected on day 0. *Seventh version of the American Joint Committee on Cancer/International Union for Cancer Control TNM staging system. §Local treatment included stereotactic radiosurgery and surgical resection.

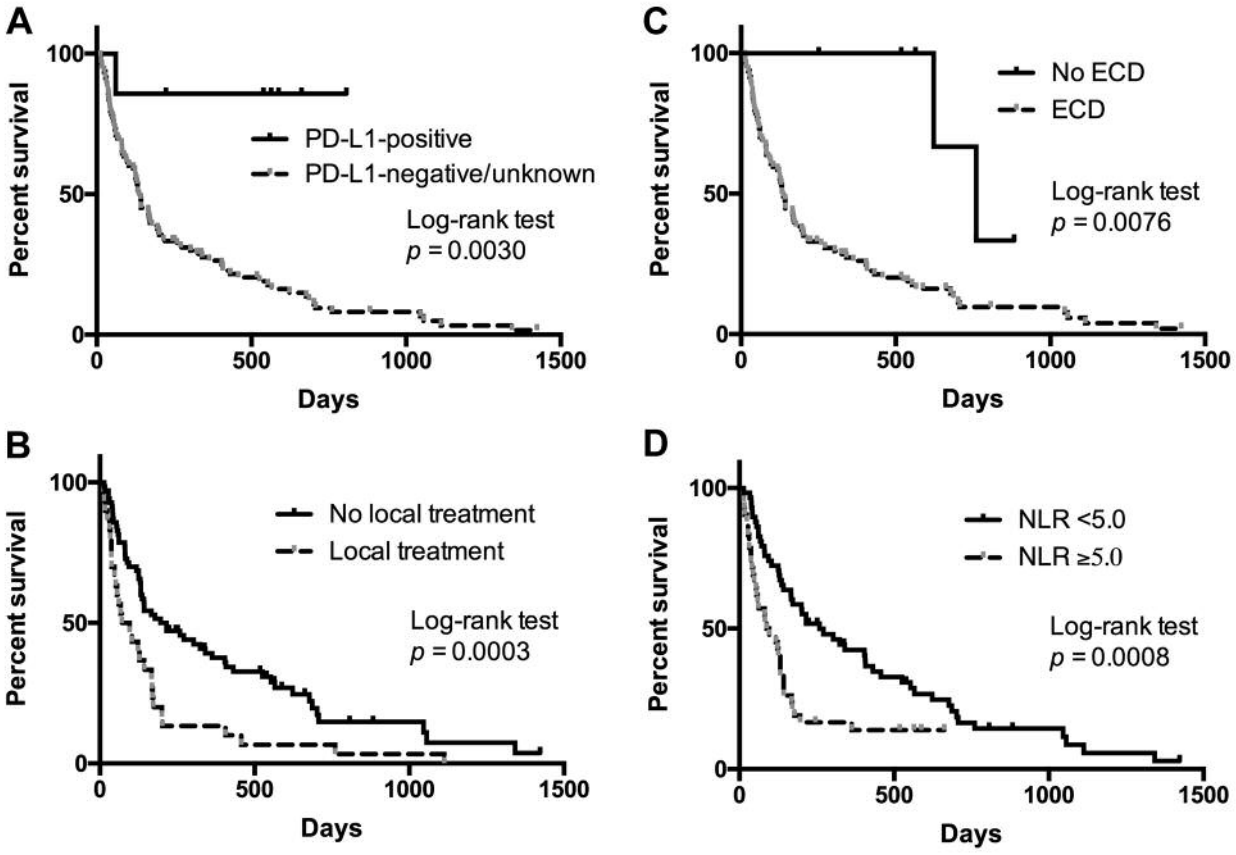

Figure 2. *Overall survival according to predictors. Overall survival curves are shown for predictors that were significant in the univariate and multivariate analyses: programmed death-ligand 1 (PD-L1) expression status in the biopsy specimens (A), history of local interventions including stereotactic radiosurgery and surgery (B), extracranial disease (ECD) status (C), and serum neutrophil–to–lymphocyte ratio (NLR) (D).*

this patient population. Therefore, we speculate that the pre-treatment NLR can help identify patients with BM who should receive WBRT.

Our univariate and multivariate analyses revealed that better survival was associated with PD-L1 expression, no history of local therapy (SRS/surgery) for BMs, and no extracranial disease. Epidermal growth factor receptor (*EGFR*) mutation- and anaplastic lymphoma kinase (*ALK*) rearrangement-positive status were not apparently associated with survival. However, the applicability of these gene statuses and PD-L1 expression to WBRT remains controversial. Most previous reports have indicated that *EGFR* mutation and *ALK* rearrangement predict good survival among patients with BMs (15). Robin *et al*. reported favorable outcomes after SRS for multiple metastases in patients with *EGFR*- and *ALK*-driven NSCLC in their relatively small retrospective study (4). We failed to detect a significant role for *EGFR* and *ALK* status when we examined WBRT in a similar population. While a meta-analysis of more than 10,000 patients with NSCLC by Zhang *et al*. indicated that PD-L1 expression was correlated with poor prognosis (16), their data included a large variety of patient backgrounds and disease stages in comparison with our study, where the cohort was more uniform with all eligible patients being diagnosed with BMs. Further prospective studies are needed to determine whether WBRT, targeted therapy, SRT, and/or SRS are preferable for patients with EGFR-, ALK-, and PD-L1- positive BMs.

The present study has several limitations, including its retrospective design, relatively small sample size, and heterogeneous patient characteristics. We included a small number of PD-L1-positive patients (n=7), including six patients who received anti-PD-1 therapy, which was associated with improved survival in the univariate analysis, but not in the multivariate analysis. In this context, patients with PD-L1-positive metastatic lung cancer are likely to receive immune checkpoint inhibitors, which could improve their survival with advanced NSCLC (7, 8). These factors may have biased our findings based on the benefits of anti-PD-1 therapy.

Conclusion

The present study revealed that an NLR of less than 5.0 and PD-L1 expression significantly predicted improved survival after WBRT for BMs from NSCLC. Prolonged survival from the start of WBRT was associated with low NLR, revealing a potent strong immune response in such patients. Since these patients may be eligible to receive WBRT plus immune checkpoint inhibitors, the potential strong immune response might result in better survival outcomes. Nevertheless, a prospective trial with a large homogeneous patient sample is needed to validate our findings.

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