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The indication of palliative whole-brain radiotherapy for patients with brain metastases: a simple prognostic scoring system in the era of stereotactic radiosurgery

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Abstract

Background Stereotactic irradiation has become the mainstay treatment for brain metastases (BM), and whole-brain radiotherapy (WBRT) is often used for symptom palliation. However, the survival time of patients with BM undergoing palliative WBRT (pWBRT) is limited, making it difficult to select patients who should receive treatment.

Methods We collected patient data from 2016 to 2022 at the Shizuoka Cancer Center and retrospectively analyzed the factors related to survival time. Overall survival (OS) was defined as the survival time after WBRT.

Results A total of 301 patients (median age, 66 years) who underwent pWBRT were included. The primary cancers were lung, breast, gastrointestinal tract, and other cancers in 203 (67%), 38 (13%), 33 (11%), and 27 (9%) patients, respectively. Median OS of all patients was 4.1 months. In the multivariate analysis, male sex (hazard ratio [HR]:1.4), Karnofsky Performance Status (KPS) ≤ 60 (HR:1.7), presence of extracranial metastasis (ECM) (HR:1.6), neutrophil-lymphocyte ratio (NLR) ≥ 5 (HR:1.6), and lactate dehydrogenase (LDH) ≥ upper limit of normal (ULN) (HR:1.3) were significantly associated with shorter OS (all $P < 0.05$). To predict the OS, we created a prognostic scoring system (PSS). We gave one point to each independent prognostic factor. Median OS for patients with scores of 0–2, 3, and 4–5 were 9.0, 3.5 and 1.7 months, respectively ($P < 0.001$).

Conclusions Male sex, KPS ≤ 60, presence of ECM, NLR ≥ 5, and LDH ≥ ULN were poor prognostic factors for patients with BM undergoing pWBRT. By PSS combining these factors, it may be possible to select patients who should undergo pWBRT.

Keywords Palliative whole brain radiotherapy, Brain metastases, Prognostic scoring system, Cancer

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Introduction

Brain metastases (BM) are the most common intracranial tumors, affecting up to 40% of all cancer patients [1]. Radiotherapy for BM has significantly changed in recent years. Stereotactic radiotherapy (STI) has become the standard treatment for patients with BM [2, 3]. In addition, the effects of targeted therapy [4] and immune checkpoint inhibitors [5] on BM have been shown. As a result, whole-brain radiotherapy (WBRT) is often used as a palliative treatment for patients with BM who are not candidates for systemic therapy, tumor resection or STI [6]. It has been reported in the QUARTZ trial that palliative WBRT (pWBRT) did not provide a clear benefit for patients with BM that have poor survival outcomes [7]. However, patients who survived longer than six months after WBRT showed significant improvements in physical and emotional functioning [8]. Therefore, patients with reasonable life expectancies should not be excluded from pWBRT, and the selection of patients for pWBRT is significant.

Several studies have attempted to identify the prognostic factors and predict the life expectancy of patients with BM. The recursive partitioning assessment (RPA) [9] and graded prognostic assessment (GPA) scores [10] are well known, which are based on clinical characteristics such as the patient age, Karnofsky Performance Status (KPS), status of extracranial disease, and number of BM. However, it is difficult to predict the patient prognosis based on clinical factors alone [11]. Blood tests can provide an objective measure of the current status of patients, which has recently been shown to correlate with outcomes in several cancers. For example, the neutrophil-lymphocyte ratio (NLR), which reflects systemic inflammation, is a predictor of overall survival (OS) after craniotomy [12] or STI [13] for BM, and lactate dehydrogenase (LDH), which may reflect high tumor load, is also a predictor of OS in patients with BM [14]. To predict the life expectancy of patients with BM, it may be helpful to combine the clinical characteristics and laboratory parameters of patients.

Herein, we collected patient data from 2016, when STI began to be used at our institute, to 2022, and retrospectively analyzed factors related to survival time after pWBRT. This study aimed to create a prognostic scoring system (PSS) for patients with BM treated with pWBRT.

Method

Patient population

All analyses were approved by the Institutional Review Board of Shizuoka Cancer Center (J2023-174-2023-1-3) and was conducted in accordance with the principles of the Declaration of Helsinki.

We retrospectively studied 580 consecutive patients who underwent WBRT at the Shizuoka Cancer Center between June 2016, which was when STI began to be used for BM with more than four lesions, and December 2022. All patients were diagnosed with BM using magnetic resonance imaging or computed tomography scan. We excluded patients with primary brain tumor, hematological malignancy, pediatric patients under the age of 15 years, post-resection BM, prophylactic irradiation for SCLC, and meningeal metastasis.

The clinical data of patients included date of birth, sex, height, body weight, past medical history, KPS, first date of WBRT, date of death or last visit, primary site of the lesion, number of BM, presence of extracranial metastasis (ECM), and regular use of oral steroids for >4 weeks. Blood tests were performed 1 month before WBRT without intravenous steroid injection. Neutrophil, lymphocyte, serum albumin levels, LDH, and hemoglobin (Hb) were recorded. Because NLR≥5 [12], serum albumin<lower limit of normal (LLN), Hb<LLN, and LDH>upper limit of normal (ULN) [14] have been reported to be prognostic factors for patients with BM, we defined these values as the respective thresholds.

Treatment

The cancer board of our institution approved WBRT for patients with the following characteristics: (1) patients unsuitable for resection and STI, and (2) a life expectancy of ≥3 months based on the evaluation of the medical oncologists. The prescribed dose was calculated at the isocenter of the radiation field. The WBRT treatment plan included a total dose of 30 Gy in 10 fractions for 261 patients (87%), 30 Gy in 12 fractions for 16 patients (5%), 37.5 Gy in 15 fractions for 13 patients (4%), and others for 11 patients (4%).

Statistical analysis

The OS was calculated from the first date of WBRT to the date of death due to any cause or the last visit to our hospital. Prognostic factors were analyzed using the log-rank test and Bonferroni correction for the univariate analysis and Cox regression analysis for the multivariate analysis. Statistical significance was set at $P<0.05$. Statistical analysis was performed using the EZR statistical software (version 1.63) [15].

Results

Patient characteristics

A flowchart of the patient selection process is shown in Fig. 1. A total of 580 patients who underwent WBRT were analyzed, and 279 patients were excluded for the following reasons: primary brain tumor, 27; meningeal metastasis, 21; prophylactic WBRT for SCLC, 105; hematological malignancy, 21; post-resection of BM, 63; pediatric patient, 20; and unavailable blood data, 22. Finally, 301 patients who underwent pWBRT were included

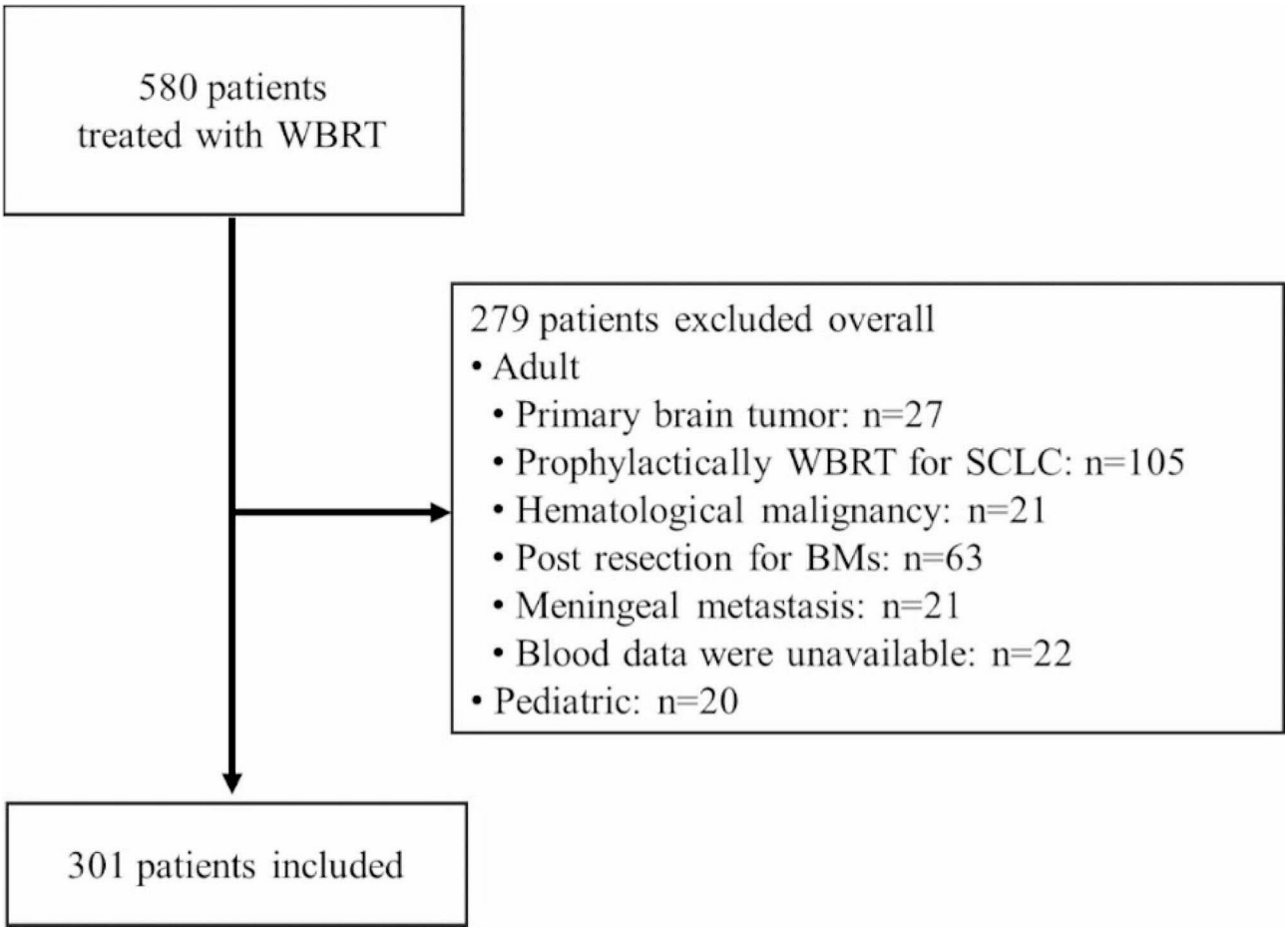

Fig. 1 The patient selection flowchart. BM, brain metastases; SCLC, small cell lung cancer; WBRT, whole-brain radiotherapy

in this study. Two hundred seventy patients (90%) had died,14 patients were alive, and 17 patients were lost to follow-up. The Patient characteristics are shown in Table 1. The median follow-up duration was 3.9 months (interquartile range, 1.6–9.9), and the median age at the first day of WBRT was 66 years (range, 22–87). The patients with age≥60 years, of male sex, a KPS≥70, and with an ECM were 211 (70%), 171 (57%), 155 (51%), and 245 (81%), respectively. The primary cancers were lung, breast, gastrointestinal, gynecological, and other cancers in 203 (67%), 38 (13%), 33 (11%), 8 (3%), and 19 (6%) patients, respectively. The median NLR and serum albumin level, LDH and Hb before WBRT were 3.6 (range, 0.26–49) and 3.8 (range, 1.9–5.2), 235 (range, 122–4665) and 12.2 (range, 4.0-17.5) respectively.

Univariate and multivariate analyses of the OS

Figure 2A presents the Kaplan–Meier survival curves for patients with BM treated with WBRT. The median OS for all patients was 4.1 months (95% confidence interval [CI]: 3.3–4.7 months). Table 2 shows the factors associated with the OS. In the univariate analysis, the factors associated with a shorter OS were male sex (median OS, 3.2 months; 95% CI: 2.3–4.0 months, $P<0.01$), KPS≤60 (median OS, 2.4 months; 95% CI: 2.0–3.1 months, $P<0.01$), not lung cancer (median OS, 2.8 months; 95% CI: 2.0–3.6 months, $P=0.02$), presence of ECM (median OS, 3.6 months; 95% CI: 2.9–4.3 months, $P=0.04$), NLR≥5 (median OS, 2.2 months; 95% CI: 1.8–2.6 months, $P<0.01$), serum albumin<3.5 (median OS, 2.1 months, 95% CI: 1.6–2.4 months, $P<0.01$), LDH>ULN (median OS, 2.5 months, 95% CI: 2.1–3.1 months, $P<0.01$) and Hb<LLN (median OS, 2.9 months, 95% CI: 2.4–3.7 months, $P<0.01$). RPA was a significant predictor of prognosis, but GPA was not. Driver gene mutations such as EGFR/ALK/ROS1 were not significant prognostic factors in patients with non-SCLC ($P=0.56$). In the multivariate analysis, the factors associated with a shorter OS were male sex (hazard ratio [HR]: 1.4, 95% CI: 1.1–1.8, $P=0.01$), KPS≤60 (HR: 1.7, 95% CI: 1.3–2.2, $P<0.01$), presence of ECM (HR: 1.6, 95% CI: 1.1–2.2, $P<0.01$), NLR≥5 (HR: 1.6, 95% CI: 1.2–2.1, $P<0.01$), and LDH>ULN (HR: 1.3, 95% CI: 1.0–1.7, $P=0.03$). The Kaplan–Meier curves for these factors are shown in Fig. 2B and F. Since we aimed to establish a PSS that can

Table 1 Patient characteristics

		N	(%)
Age	≥60	211	(70%)
(Median: 66)	<60	90	
Sex	Male	171	(57%)
	Female	130	
KPS	≥70	155	(51%)
	≤60	146	
Primary site	Lung	203	(67%)
	Breast	38	(13%)
	Gastrointestinal	33	(11%)
	Gynecologic	8	(3%)
	Others	19	(6%)
ECM	Present	245	(81%)
	Absent	56	
Diabetes Mellitus	Yes	33	(11%)
	No	268	
Steroid	Yes	44	(15%)
	No	257	
Hemoglobin	≤LLN	161	(53%)
(Median: 12.2)	> LLN	140	
NLR	≥5	96	(32%)
(Median: 3.6)	<5	205	
Serum albumin	< LLN	75	(25%)
(Median: 3.8)	≥LLN	226	
LDH	≥ULN	122	(41%)
(Median: 235)	< ULN	179	

KPS, Karnofsky performance status; ECM, extracranial metastasis; LDH, lactate dehydrogenase; LLN, lower limit of normal; NLR, neutrophil-lymphocyte ratio; ULN, upper limit of normal

be used regardless of primary cancer, the primary site was not included as a factor in the multivariate analysis.

Prognostic scoring system for patients with BM treated with pWBRT

A new PSS was introduced to predict the survival of patients after pWBRT. The PSS was associated with male sex and the presence of ECM, KPS, NLR, and LDH, which were independent prognostic factors. A score of one was assigned to male sex, presence of ECM, KPS≤60, NLR≥5, and LDH>ULN, and a score of zero to female sex, absence of ECM, KPS≥70, NLR<5, and LDH≤ULN. Since the HR of each variable was almost equivalent, the weights of the assigned scores were set equally among these factors. The Kaplan–Meier survival curve showed that the median duration of OS for 129 patients with a score of 0–2, 89 patients with a score of 3 and 83 patients with a score of 4–5 were 9.0 (95% CI: 6.4–10.4), 3.5 (95% CI: 2.8–4.7) and 1.7 months (95% CI: 1.3–2.1), respectively ($P<0.001$; Fig. 2G; Table 3). Lung cancer patients were almost equally included in each group.

Discussion

The purpose of WBRT has changed to palliation due to STI having an increased use for the treatment of BM. In recent years, the prognosis of patients undergoing pWBRT has been reported to be poor at 2.8–3.7 months [16, 17]. In our study, the median OS of patients receiving pWBRT was also poor (4.1 months), which is consistent with previous reports. Since the effectiveness of palliation has been confirmed in patients who survive for more than half a year after WBRT [8], patients who can survive for a long time should be selected. The Radiation Therapy Oncology Group reported the RPA [9] and GPA [10] as prognostic tools for cancer patients with BM. However, the treatment methods for BM have changed significantly since the publication of these reports. Therefore, we believe that it would be meaningful to create a prognostic tool that is limited to patients with BM who are undergoing pWBRT.

In this study, male sex, presence of ECM, KPS≤60, NLR≥5, and LDH>ULN were significant poor prognostic factors for patients undergoing pWBRT based on the multivariate analysis. In a retrospective analysis of 239 patients with BM who received pWBRT, male sex was reported to be a poor prognostic factor [17], similar with our results. The KPS, although no significant difference was found in the QUARTZ trial, tended to be related to patient prognosis [7]. The KPS has been reported to be an independent predictive factor in non-SCLC patients with BM who underwent pWBRT [18]. In addition, the KPS is a prognostic factor for terminally ill cancer patients [19, 20]. Regarding the NLR≥5, patients with a low NLR may experience prolonged survival after WBRT for advanced non-SCLC [21]. Similarly, the NLR has been reported to be a prognostic factor after resection [12] and radiation therapy [13] in patients with BM. To the best of our knowledge, this is the first study to examine the NLR in patients with cancer who underwent pWBRT. LDH was reported to be a factor in the LabBM score, which was reported in a cohort of 1200 cancer patients with BM [14]. LDH may reflect high tumor load and inflammation. LabBM score consists of Hb, platelet count, LDH, C-reactive protein (CRP) and serum albumin. Because systemic inflammation was reported to be associated with cancer development and progression [13], NLR, LDH, and CRP may be important factors in the cancer journey. Hence, blood tests can provide an objective measure of the current status of patients. Because CRP data was missing in 10% of patients, CRP could not be analyzed in this study. To create a PSS for patients with BM who receive pWBRT, the combination of the clinical characteristics and laboratory parameters of patients may be better.

We created a PSS for patients with BM who had undergone pWBRT. This PSS consisted of male sex and the

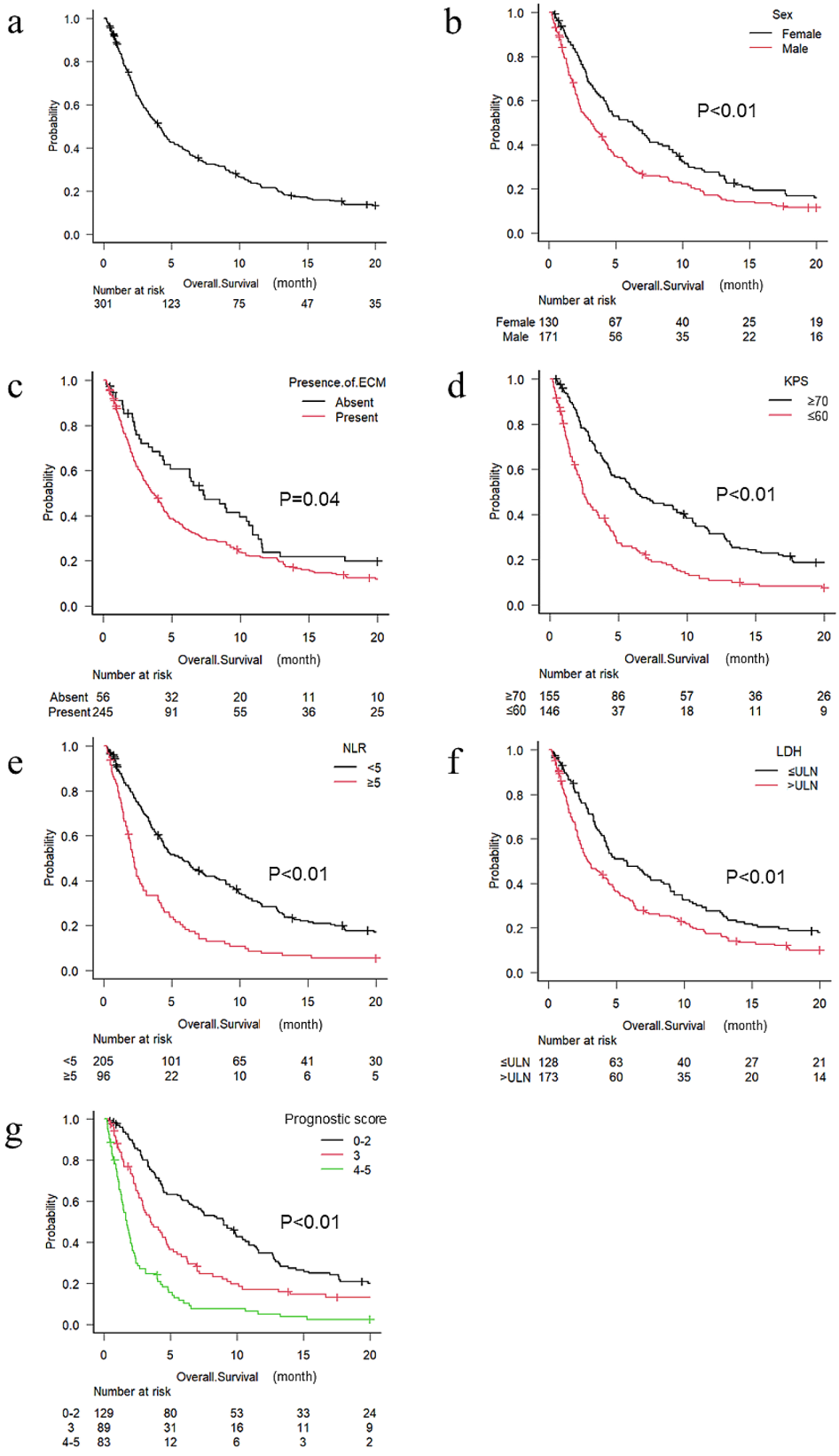

Fig. 2 Kaplan–Meier curves of the overall survival. **a**. All patients. **b**. Sex of the patients. **c**. Presence of extracranial metastasis. **d**. Karnofsky performance status ≥ 70 or ≤ 60. **e**. Neutrophil-lymphocyte ratio ≥ 5 or < 5. **f**. Lactate dehydrogenase ≥ upper limit of normal or < upper limit of normal. **g**. Prognostic score 0–2, 3 and 4–5

Table 2 Univariate and multivariate analysis of the OS

	N	Median OS	Univariate analysis		Multivariate analysis		
			95% CI	*P*-value	HR	95% CI	*P*-value
Total	301	4.1					
Age							
< 60	90	4.2	3.1–5.8	0.95			
≥ 60	211	4.1	3.0–4.8				
Sex							
Male	171	3.2	2.3–4.0	**< 0.01**	1.4	1.1–1.8	**0.01**
Female	130	6.3	4.3–7.5				
KPS							
≤ 60	146	2.4	2.0–3.1	**< 0.01**	1.7	1.3–2.2	**< 0.01**
≥ 70	155	6.3	4.4-9.0				
Primary site							
Lung	203	4.7	4.0-6.2	**< 0.01**			
Breast	38	7.3	3.3–14.0				
Gastrointestinal	33	1.8	1.3–2.7				
Gynecologic	8	2.8	1.1–6.4				
Others	19	2.2	1.4–4.2				
Number of BM							
≤ 4	53	3.4	2.0–4.4	0.57			
5–9	64	4.0	2.7–6.4				
≥ 10	184	4.3	3.2–5.8				
Presence of ECM							
Present	245	3.6	2.9–4.3	**0.04**	1.6	1.1–2.2	**< 0.01**
Absent	56	7.3	4.4–10.6				
Diabetes Mellitus							
Yes	33	2.6	2.3–5.1	0.43			
No	268	4.2	3.5–4.8				
Steroid							
Yes	44	3.7	2.2–5.2	0.68			
No	257	4.2	3.4–4.8				
NLR							
≥ 5	96	2.2	1.8–2.6	**< 0.01**	1.6	1.2–2.1	**< 0.01**
< 5	205	5.8	4.3–7.3				
Serum albumin							
< 3.5	75	2.1	1.6–2.4	**< 0.01**	1.3	1.0–1.8	0.08
≥ 3.5	226	4.9	4.2–6.3				
LDH							
≥ULN	122	2.5	2.1–3.1	**< 0.01**	1.3	1.0-1.7	**0.03**
< ULN	179	5.8	4.2–7.1				
Hemoglobin							
< LLN	161	2.9	2.4–3.7	**< 0.01**	1.3	1.0-1.7	0.053
≥LLN	140	5.2	4.3–7.2				
RPA							
I	5	11.6	10.4–N/A	**< 0.01**			
II	150	5.9	4.4–8.9				
III	146	2.4	2.0–3.1				
GPA							
0–1	208	3.4	2.7–4.1	0.09			
1.5–2.5	87	6.3	4.3–9.8				
3	6	10.0	0.6–N/A				

Bold values indicate statistical significance set at $P < 0.05$

BM, brain metastasis; CI, confidence interval; ECM, extracranial metastasis; GPA, graded prognostic assessment; HR, hazard ratio; KPS, Karnofsky performance status; LDH, lactate dehydrogenase; LLN, lower limit of normal; N/A, not applicable; NLR, neutrophil-lymphocyte ratio; OS, overall survival; RPA, recursive partitioning assessment; ULN, upper limit of normal

Table 3 The details of the prognostic scoring system for patients with brain metastases treated with palliative whole brain radiotherapy

Score	*N*	Lung cancer (%)	Median OS	95%CI	*P*-value
0–2	129	92 (71%)	9.0	6.4–10.4	< 0.01
3	89	62 (70%)	3.5	2.8–4.7	
4–5	83	49 (59%)	1.7	1.3–2.1	

N, number; OS, overall survival; CI, confidence interval

presence of ECM, KPS, NLR, and LDH, which were independent prognostic factors based on the analyses. We assigned one point to each factor and created a simple PSS. The median OS for patients with a score 0–2, those with score 3 and those with score 4–5 were 9.0, 3.5 and 1.7 months, respectively. This PSS may be useful for predicting patients who will survive for more than half a year. Based on the results of the QUARTZ trial, patients with a score of 0–2 may be recommended pWBRT and patients with a score of 4–5 may be recommended best care support. Recently, a multicenter retrospective study conducted in Spain reported a prognostic index for patients with BM treated with pWBRT [17]. The study showed seven factors that are necessary for predicting patient prognosis, such as ECOG PS≥2, digestive cancer, urothelium cancer, prior WBRT, absence of systemic treatment after WBRT, history of targeted treatment prior to BM, and high CRP value. The study assigned 1–3 points to each factor and divided them into three groups: good, intermediate, and poor prognosis. Compared to their report, our study may be more easily used in clinical practice because of the simplified scoring and grouping of patients. Although we believe that chemotherapy, targeted therapy, and immune checkpoint inhibitors before and after pWBRT are important factors, we were unable to collect such data for some cases in this study.

This study had some limitations. The analyzed data were obtained from a single facility, and there was a risk of patient selection bias. Although the sample size was sufficient for the statistical analysis, the results were not validated. In the future, we need to validate this PSS in patients with BM from multiple centers. The blood test results, such as CRP levels, should have been analyzed, but were excluded from the analysis because they could not be collected from some patients.

Conclusion

Male sex, KPS≤60, presence of ECM, NLR≥5, and LDH>ULN were poor prognostic factors for patients with BM who underwent pWBRT. By PSS combining these factors, it may be possible to select patients who should undergo pWBRT. In the future, we need to validate this PSS in patients with BM from multiple centers.

Abbreviations

BM	Brain metastases
CI	Confidence interval
CRP	C-reactive protein
ECM	Extracranial metastasis
GPA	Graded prognostic assessment
Hb	Hemoglobin
HR	Hazard ratio
KPS	Karnofsky performance status
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
NLR	Neutophil-lymphocyte ratio
OS	Overall survival
PSS	Prognostic scoring system
pWBRT	Palliative whole brain radiotherapy
RPA	Recursive partitioning assessment score
SCLC	Small cell lung cancer
STI	Stereotactic irradiation
ULN	Upper limit of normal
WBRT	Whole brain radiotherapy

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Author contributions

All the authors contributed to the design and conception of this study. TH and SD conducted the data collection and analysis, and prepared the first draft of the manuscript. All authors commented on and critically revised previous drafts of the manuscript, and approved of the final manuscript.

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Data availability

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of Shizuoka Cancer Center (J2023-174-2023-1-3) This study collected data from hospital medical records from the period of June 2016 and December 2022. The need for written informed consent was waived by the Shizuoka Cancer Center ethics committee due to the retrospective nature of the study. This study neither contains personal information nor involves commercial interests.

Competing interests

The authors declare no competing interests.

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