Serum lactate dehydrogenase predicts survival in small-cell lung cancer patients with brain metastases that were treated with whole-brain radiotherapy

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Introduction

Small-cell lung cancer (SCLC) represents <20% of total lung cancer cases [1]. The survival outcome for this malignancy is poor, with a 2-year survival rate of ~20–40% and <10% for patients with limited disease (LD) and extensive disease (ED), respectively [2, 3]. The most important prognostic factors in SCLC are disease stage, clinical performance status (PS), and lactate dehydrogenase (LDH) levels [4–6].

SCLC patients often develop brain metastases (BMs) over the course of the disease. The incidence of BMs at the time of diagnosis for SCLC is reported to be 10–14% [7]. In addition, up to 50% of patients with SCLC eventually develop BMs [8]. Prophylactic cranial irradiation (PCI) has become a standard of care in decreasing the incidence of brain failure and improving the survival for SCLC patients with LD [9]. For clinically involved BMs, whole-brain radiotherapy (WBRT) is preferred for treatment, since this modality offers intracranial tumor control and palliation for multiple BMs from SCLC, as recommended by Japanese guidelines [10].

There are several well-established models for predicting the prognosis of patients with BMs, such as the Radiation Therapy Oncology Group—recursive partitioning analysis (RTOG-RPA) and graded prognostic assessment (GPA) [11, 12]. These predictive models include the patients with SCLC (<10% of the all assessed patients). Therefore, specific predictors for outcomes associated
with SCLC and BMs remain unclear. Recently, in the quality of life after treatment for brain metastases (QUARTZ) study, no differences in both quality-adjusted life-years and overall survival were observed between best supportive care (BSC) alone and BSC plus WBRT in non–small-cell lung cancer (NSCLC) patients with BMs [13]. Thus, prognostic indicators for survival should be clarified in SCLC patients with BMs to exclude patients with very poor prognosis from clinical studies on WBRT.

The purpose of the present study was to identify prognostic factors for response to WBRT among patients with BMs from SCLC.

**MATERIALS AND METHODS**

**Patients**

The protocol of this retrospective study was approved by our institutional review board (30–028), with all patients providing informed consent for WBRT. Between February 2008 and December 2017, we identified 53 consecutive patients with BMs from SCLC who underwent WBRT at our institution. We excluded patients who had follow-up durations of <90 days without any specific events. In addition, patients who had a past treatment history of BMs were excluded from this study; this included 3 patients, 1 patient and 1 patient who underwent surgical resection, stereotactic radiosurgery (SRS) and PCI, respectively. Therefore, a total of 48 patients were eligible for this analysis. The characteristics of the study patients are shown in Table 1. All patients had pathologically confirmed SCLC with a diagnosis of BMs, which was based on findings from computed tomography (CT) and/or magnetic resonance imaging (MRI). Blood test data between 4 weeks before the WBRT and the first day of WBRT treatment were available. When WBRT was initiated, all patients except one had primary or extracranial metastatic lesions in regions such as bones, adrenal glands, and the liver.

The median patient age was 70 years; 42 (88%) and 6 (13%) patients were male and female, respectively. At the initial staging, 32

| Clinicopathological characteristic | Patients (n = 48) |
|-----------------------------------|------------------|
| Age (years) [median (range)]      | 69.5 (47–90)     |
| Sex, n (%)                        |                  |
| Male                              | 42 (88)          |
| Female                            | 6 (13)           |
| Smoking (pack years) [median (range)] | 55 (0.3–230)          |
| ECOG-PS, n (%)                    |                  |
| 0                                 | 16 (33)          |
| 1                                 | 12 (25)          |
| 2                                 | 15 (31)          |
| 3                                 | 4 (8)            |
| 4                                 | 1 (2)            |
| Stage at initial diagnosis, n (%) |                  |
| Limited disease                   | 16 (33)          |
| Extensive disease                 | 32 (67)          |
| Brain metastases at presence      | 22 (46)          |
| Duration between the initial diagnosis and the first appearance of BMs a (days) [median (range)] | 175.5 (0–1697) |
| Maximum diameter of BMs (mm) [median (range)] | 14 (1–41) |
| Number of BMs, n (%)              |                  |
| 1                                 | 9 (19)           |
| 2                                 | 10 (21)          |
| 3                                 | 3 (6)            |
| 4                                 | 8 (17)           |
| 5                                 | 1 (2)            |
| ≥6                                | 17 (35)          |
| Total prescription doses (Gy)     | 30 (30–40)       |
| Number of fractions [median (range)] | 10 (10–16)       |
| BED_{10} (Gy) [median (range)]    | 39 (39–50)       |
| RPA class, n (%)                  | 29 (60)          |

**Table 1. Continued**

| Clinicopathological characteristic | Patients (n = 48) |
|-----------------------------------|------------------|
| GPA score, n (%)                  |                  |
| 0.0                               | 9 (19)           |
| 0.5                               | 12 (25)          |
| 1.0                               | 13 (27)          |
| 1.5                               | 7 (15)           |
| 2.0                               | 7 (15)           |

ECOG-PS = Eastern Cooperative Oncology Group performance status, BMs = brain metastases, RTOG-RPA = Radiation Therapy Oncology Group–recursive partitioning analysis, GPA = graded prognostic assessment. BMs at the initial diagnosis was considered as Day 0.
and shows overall survival after WBRT treatment. The ratio of 10 Gy for tumor tissue. The median biologically effective dose (BED) was 39 (range: 39–763 days). Symptoms due to BMs were observed in 25 patients (60%), 16 (33%) and 16 (33%) patients had ED and LD SCLC, respectively. In addition, 22 (46%) patients had BMs at the time of the initial diagnosis of SCLC. Twenty-eight (58%) had good general condition, as indicated by an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1, and 20 (42%) patients had a poor general condition (ECOG-PS of 2 or worse). The median diameter of BMs was 14 mm (1–41 mm). The median pre-WBRT serum LDH levels were 227.5 (140–998 u/l), the neutrophil-to-lymphocyte ratio (NLR) was 2.20 (0.40–26.43), the platelet-to-lymphocyte ratio (PLR) was 137.04 (33.65–802.38) and C-reactive protein (CRP) was 0.45 (0.02–7.26 mg/dl). Twenty-nine (60%) and 19 patients (40%) were classified as RPA Class 2 and 3, respectively; no patient had an RPA class of 1.

All patients were typically treated with WBRT using conventional external beam radiotherapy at a photon energy of 4, 6 or 10 MV and lateral-opposed treatment fields that encompassed the entire brain. The prescribed dose was calculated at the isocenter of the radiation fields based on daily treatments. Thirty-three (69%), 6 (13%) and 9 (19%) patients received the prescribed total dose of 30 Gy in 10 fractions, 37.5 Gy in 15 fractions and 40 Gy in 16 fractions, respectively. The median biologically effective dose (BED) was 39 (range: 39–50) Gy, when prescription doses were corrected to the BED using the linear–quadratic model with an assumed α/β ratio of 10 Gy for tumor tissue.

Statistical analysis
Data are reported as the median (range) or number (percentage). Time-to-event analyses were performed from the start of WBRT to the emergence of the event. The Kaplan–Meier method and the log-rank test were used to compare the curves for overall survival. Potential prognostic factors were evaluated using the Cox proportional hazards model, and the results were reported as hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). Significant factors that were identified 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 <0.05.

RESULTS
Of the eligible 48 patients, 40 died during the follow-up period, 2 were still alive at the time of writing this report, and 6 were lost to follow-up. Of the 40 patients who died during follow-up, 4 died due to BMs, including carcinomatous meningitis and BM hemorrhage in 3 patients and 1 patient, respectively; 31 patients died due to extracranial disease; and the remaining 5 patients died due to other diseases, including pneumonia. Two patients were still alive at the end of the follow-up period (2061 and 385 days, respectively). Six patients were lost to follow-up, with a median follow-up period of 268 days (range: 181–763 days). Symptoms due to BMs were observed in 25 (52%) patients. Of the 25 patients with symptomatic BMs, 16 (64%) showed symptom improvement after WBRT.

Figure 1 shows overall survival after WBRT treatment. The median survival was 232 days and the 1- and 2-year overall survival rates were 34.4% and 5.8%, respectively. Fourteen patients (29%) developed intracranial failure after WBRT, and their median intracranial failure term was 212 days (range: 80–401 days). The results of the univariate analysis are shown in Table 2 and Fig. 2. The upper limit of the normal range was chosen as the cut-off value for LDH based on the results of the evaluation of various cut-off values (Supplementary data). Univariate analyses revealed that longer survival was associated with five factors: ECOG-PS of 0–1 (P < 0.01), asymptomatic BMs (P < 0.01), LDH levels in the normal range (P < 0.01), RTOG-RPA Class 2 (P < 0.01), and a GPA score of ≥1.5 (P < 0.05). In patients with normal and elevated LDH values, the 1-year survival rate was 54.7% and 17.6%, respectively. No significant impact on survival after WBRT was observed for the clinical stage at the initial diagnosis, presence of BMs at the initial diagnosis, maximum diameter of BMs, number of BMs, prescription dose of WBRT (Gy), or the pre-WBRT serum levels of NLR and PLR.

The results of multivariate analyses are shown in Table 3. Elevated LDH levels (P < 0.05) and presence of symptoms due to BMs (P < 0.05) were identified as significant independent predictors of poor survival.

DISCUSSION
There are various factors that can predict prognosis for BMs from various solid tumors, such as RTOG-RPA, and GPA [11, 12, 14–16]. In addition, Miyazawa et al. reported that elevated serum LDH is an independent predictor of poor survival in patients with BMs from various primary tumors [14]. Our data seem to be consistent with their results. However, in contrast to the present study, their report included small-cell carcinoma of pathological background at only 14%. Moreover, we have confirmed the utility of the GPA score and RPA class in univariate analyses, although no significant differences were found in the multivariate analysis. For these reasons, we believed that these SCLC patients had uncontrolled extracranial metastases; therefore, the RPA score inevitably increased and the GPA score decreased. Thus, predictive factors for prognosis after WBRT for BMs from SCLC remain poorly understood and should be elucidated in future studies. In this study, SCLC patients with BMs who received...
### Table 2. Univariate analysis for overall survival

| Clinicopathological parameter | Patients (n = 48) | 1-year survival rate (%) | HR (95% CI) | P-value |
|-------------------------------|------------------|--------------------------|-------------|---------|
| **Age (years)**               |                  |                          |             |         |
| <65                           | 9                | 29.6                     | 1           | 0.69    |
| ≥65                           | 39               | 35.2                     | 0.85 (0.41–2.00) |         |
| **Sex**                       |                  |                          |             |         |
| Male                          | 42               | 29.9                     | 1           | 0.15    |
| Female                        | 6                | 66.7                     | 0.49 (0.15–1.26) |         |
| **ECOG-PS**                   |                  |                          |             |         |
| 0, 1                          | 28               | 55.7                     | 1           | <0.01   |
| ≥2                            | 20               | 10.0                     | 3.45 (1.71–7.24) |         |
| **Smoking** (pack years)      | (n = 47)         |                          |             |         |
| <30                           | 6                | 33.3                     | 1           | 0.78    |
| ≥30                           | 41               | 33.7                     | 1.14 (0.49–3.35) |         |
| **Clinical stage at the initial diagnosis** | | | | |
| Limited disease               | 16               | 50.0                     | 1           | 0.34    |
| Extensive disease             | 32               | 23.9                     | 1.38 (0.72–2.75) |         |
| **Presence of BMs at the initial diagnosis** | | | | |
| Yes                           | 22               | 28.9                     | 1           | 0.87    |
| No                            | 26               | 37.5                     | 0.95 (0.51–1.81) |         |
| **Duration between the initial diagnosis and the first appearance of BMs (days)*** | | | | |
| <175                          | 23               | 27.7                     | 1           | 0.71    |
| ≥175                          | 25               | 39.0                     | 0.89 (0.47–1.69) |         |
| **Symptoms due to BMs**       |                  |                          |             |         |
| yes                           | 25               | 8.0                      | 1           | <0.01   |
| no                            | 23               | 69.6                     | 0.25 (0.12–0.49) |         |

### Table 2. Continued

| Clinicopathological parameter | Patients (n = 48) | 1-year survival rate (%) | HR (95% CI) | P-value |
|-------------------------------|------------------|--------------------------|-------------|---------|
| **Maximum diameter of BMs (cm)** |                  |                          |             |         |
| <3                            | 41               | 35.8                     | 1           | 0.22    |
| ≥3                            | 7                | 28.6                     | 1.75 (0.70–3.83) |         |
| **Number of BMs**             |                  |                          |             |         |
| ≤3                            | 22               | 43.3                     | 1           | 0.13    |
| >3                            | 26               | 26.2                     | 1.65 (0.87–3.18) |         |
| **Radiotherapeutic dose (BED_{10}), Gy** | | | | |
| <40                           | 33               | 30.3                     | 1           | 0.52    |
| ≥40                           | 15               | 43.8                     | 0.80 (0.40–1.54) |         |
| **LDH**                       |                  |                          |             |         |
| ≤ULN                          | 22               | 54.7                     | 1           | <0.01   |
| >ULN                          | 26               | 17.6                     | 2.62 (1.37–5.19) |         |
| **NLR**                       |                  |                          |             |         |
| <3.0                          | 29               | 39.4                     | 1           | 0.10    |
| ≥3.0                          | 19               | 27.1                     | 1.74 (0.90–3.36) |         |
| **PLR**                       |                  |                          |             |         |
| <137                          | 24               | 35.7                     | 1           | 0.87    |
| ≥137                          | 24               | 35.9                     | 1.05 (0.56–2.00) |         |
| **CRP**                       |                  |                          |             |         |
| <ULN                          | 13               | 35.2                     | 1           | 0.44    |
| ≥ULN                          | 35               | 34.8                     | 1.30 (0.68–2.67) |         |
| **RTOG-RPA class**            |                  |                          |             |         |
| 2                             | 29               | 53.7                     | 1           | <0.01   |
| 3                             | 19               | 10.5                     | 3.15 (1.57–6.51) |         |
| **GPA score**                 |                  |                          |             |         |
| <1.5                          | 34               | 27.2                     | 1           | <0.05   |
| ≥1.5                          | 14               | 50.0                     | 0.48 (0.21–1.00) |         |

HR = hazard ratio, CI = confidence interval, ECOG-PS = Eastern Cooperative Oncology Group performance status, BMs = brain metastases, BED = biologically effective dose, LDH = lactate dehydrogenase, ULN = upper limit of normal, NLR = neutrophil-to-lymphocyte ratio, PLR = platelet-to-lymphocyte ratio, CRP = C-reactive protein, RTOG-RPA = Radiation Therapy Oncology Group–recursive partitioning analysis, GPA = graded prognostic assessment. *BM at the initial diagnosis was considered as Day 0.

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Continued
WBRT treatment were analyzed and showed that elevated LDH and symptomatic BMs were associated with poor survival. Our findings may help assess the prognosis of SCLC patients with BMs.

Serum LDH is the enzyme that catalyzes the conversion of pyruvic acid to lactate \[17\]. LDH has been reported to be a marker for overall survival, tumor load, and cell turnover in patients with various malignancies \[18–23\]. An association between LDH and rapid proliferation of cancer cells and the tumor microenvironment has also been reported \[24–26\]. LDH could be a prognostic marker of advanced-stage cancer patients, as increased LDH levels seems to indicate the response to tissue injury due to disease state \[17\]. The determination of LDH should enter further clinical trials to confirm its relevance in cancer biology.

The presence of neurologic symptoms was another independent predictor for poor survival in this study. Gorovets et al. have reported the presence of neurologic symptoms being a determined predictor in a multi-institutional data analysis \[27\]. The finding in this study, including clinical symptoms, seems consistent with this previous report.

**Table 3. Multivariate analysis for overall survival**

| Clinicopathological parameter | Multivariate analysis |
|------------------------------|----------------------|
| ECOG-PS                      |                      |
| 0, 1                         | 1                    |
| 2–                           | 2.03 (0.10–14.79)    |
| Symptoms due to BMs          |                      |
| Yes                          | 1                    |
| No                           | 0.32 (0.12–0.79)     |
| LDH                          |                      |
| ≤ULN                         | 1                    |
| >ULN                         | 2.38 (1.20–4.86)     |
| RPA class                    |                      |
| 2                            | 1                    |
| 3                            | 0.80 (0.12–16.27)    |
| GPA score                    |                      |
| <1.5                         | 1                    |
| ≥1.5                         | 1.08 (0.41–2.66)     |

**Fig. 2. Survival of SCLC patients with BMs after whole brain radiotherapy. Asymptomatic BMs (A) and normal range of LDH (B). These factors were positive predictors, as identified in the univariate analyses. SCLC = small-cell lung cancer, BMs = brain metastases, LDH = lactate dehydrogenase, ULN = upper limit of normal.**

We first hypothesized that immune response might prolong survival after WBRT for BMs. Thus, NLR was assessed as a surrogate marker for immune responses in this study, since immune checkpoint inhibitor–based therapy has recently attracted attention for improving NSCLC patient outcomes \[28, 29\]. In addition, Kang et al. have reported the negative impact of a high NLR on survival in SCLC patients with LD who received chemoradiotherapy \[30\]. However, no relationship between NLR and survival were observed in SCLC patients with BMs in this study. In addition, a recent Phase 1/2 clinical trial failed to show therapeutic improvement of anti-programmed death-1 (PD-1) for recurrent SCLC \[31\]. SCLC has been believed to have a tumor biological background from NSCLC. However, little is known in terms of immunological differences. Thus, we hypothesize that SCLC may have different immunity characteristics from those of NSCLC.

To the best of our knowledge, only a few reports have shown LDH values as being associated with survival in SCLC patients with BMs. In the present study, we showed that high LDH levels and the existence of BM-related symptoms were associated with shorter survival in SCLC patients with BMs, and that these factors can be independent prognostic markers for WBRT candidates with metastatic
SCLC. Therefore, serum LDH can be a simple, non-invasive, and objective biomarker for survival in patients with BMs from SCLC.

The present study has several limitations, including its retrospective design, relatively small sample size, and heterogeneous patient characteristics; however, these study characteristics were similar to those of a previous study [32]. SCLC has been excluded from clinical trials of SRS and surgery because of the associated poor prognosis. WBRT has been reported as the only effective treatment for BMs from SCLC [33]. However, the QUARTZ study revealed the non-inferiority of BSC to WBRT in NSCLC patients with BMs that were unsuitable for resection or stereotactic radiotherapy [13]. Therefore, BSC might also be a suitable treatment option in patients with BMs from SCLC who have poor prognosis. On the other hand, SRS might be a reasonable treatment option for achieving favorable outcomes in SCLC patients [34, 35]. The present data would be beneficial for guiding patient selection. Therefore, further prospective study is warranted to establish an ideal treatment strategy for BMs from SCLC.

In conclusion, the present study revealed that a high LDH level and the existence of BM-related symptoms predict significantly poor survival after WBRT for BMs from SCLC.

SUPPLEMENTARY DATA
Supplementary data are available at Journal of Radiation Research online.

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