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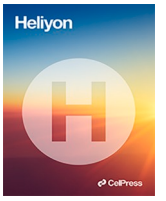

Research article

# Survival prognostic factors in nonsmall cell lung cancer patients with simultaneous brain metastases and poor performance status at initial presentation

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ABSTRACT

*Purpose:* Although the treatment of nonsmall cell lung cancer (NSCLC) has rapidly progressed recently, there is little evidence of treatment for patients with symptomatic brain metastases (BM) and poor performance status (PS). However, in symptomatic BM patients, appropriate upfront intracranial treatment can often lead to rapid improvement in PS and effective systemic therapy. Thus, this study investigated the prognostic factors for the survival of poor PS NSCLC patients with synchronous BM.

*Methods:* Data of patients with BM and Karnofsky PS (KPS) ≤70 at the first diagnosis of NSCLC who were treated in our hospital between January 2017 and December 2021 were reviewed. Patient survival was compared among patients stratified by type of first-line regimen of systemic treatment. Correlations between patient characteristics and survival were examined.

*Results:* Fifty patients receiving aggressive treatment were enrolled. The median survival times for tyrosine kinase inhibitor (TKI), immune checkpoint inhibitor (ICI), and chemotherapy alone groups were 19 (95 % confidence interval [CI], 2.8–68.5), 19 (3.0–62.0), and 13 (1.2–24.8) months, respectively. Survival in the TKI and ICI groups was significantly longer than in the chemotherapy alone group ($p = 0.046$, TKI vs. chemo; $p = 0.022$, ICI vs. chemo; $p = 0.023$). Both sex and type of systemic treatment correlated to survival time on univariate analysis. Chemotherapy alone for systemic treatment [$p = 0.034$; hazard ratio (HR), 0.44 (0.20–0.94)] remained significant for predicting overall survival in the multivariate analysis.

*Conclusion:* Even in patients with poor PS and BM at the initial diagnosis of NSCLC, the ICI group had a survival time comparable to that of the TKI group when combined with tailor-made intracranial treatment. There is a subgroup in the patient population that was previously considered unsuitable for ICI, whose PS improves with individualized intracranial treatment, and who may benefit from immunotherapy.

*Abbreviations:* NSCLC, nonsmall cell lung cancer; BM, brain metastases; KPS, Karnofsky Performance Status; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; PS, performance status; OS, overall survival; PD-L1, programmed cell death 1-ligand 1; TPS, tumor proportion score.

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## 1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with 80 % of lung cancer patients having nonsmall cell lung cancer (NSCLC) [1–6]. The proportion of patients with "poor performance status (PS)" (Eastern Cooperative Oncology Group (ECOG)-PS $\geq$ 2) at initial diagnosis is reported to be 48 % among those with advanced NSCLC, and many of these patients without genetic mutations are unable to benefit from advanced systemic therapy [7,8]. Patients with poor PS and symptomatic brain metastases (BM) have been excluded from many clinical trials on systemic therapy and are considered a challenging population with little evidence for treatment. However, it is often experienced that PS improves rapidly in such patients with symptomatic synchronous BM due to the resolution of neurological symptoms after intracranial treatment.

More than half of patients with poor PS at initial presentation have BM, which is one of the most common causes of poor PS [9]. Despite the high frequency of metastatic brain tumors among all brain tumors (17.4 %) [10–14], management of intracranial metastases is currently left mainly to the physician responsible for systemic treatment. The course of neurological symptoms is therefore not often individually predicted by tumor location, with treatment plans based primarily on the size and number of metastatic sites.

Particularly, immunotherapy requires an individualized treatment strategy due to the slightly slower onset of therapeutic effect in lesions, restrictions regarding steroid use and problems with pseudoprogression, and various additional limitations regarding intracranial therapy. It was reported that among patients with poor PS for whom immunotherapy is not recommended under current guidelines, some patients respond to treatment and have relatively long survival, and studies are underway to explore the characteristics of these patient populations. Recently, it was reported that survival time varies greatly depending on the primary condition that determines the ECOG-PS, i.e., tumor burden or comorbidity [15–17]. A prognosis study involving NSCLC patients with PS2 reported a notable effect of immunotherapy [18]. Since the clinical behavior of BM depends on the subsequent systemic treatment, the clinical outcome of metastatic brain tumors must be investigated, taking into account the differences among systemic treatments [19].

The current study aimed to investigate the survival of poor PS patients with synchronous BM of NSCLC receiving systemic treatment and to investigate the prognostic factors for survival.

## 2. Material and methods

### 2.1. Study design and participants

For this retrospective, single-center study, data of all patients with BM with Karnofsky Performance Status (KPS) $\leq$70 at the time of initial diagnosis of NSCLC who were treated in our hospital between January 2017 and December 2021 were reviewed. All clinical data were extracted from the electronic health record for this analysis. All enrolled patients provided informed consent. Moreover, they were anonymized and their data remained confidential. This study was conducted with approval by the local research ethics committee of our hospital (2019-3).

### 2.2. Patient characteristics

Patient data, including patient age, sex, KPS both at arrival and after intracranial local treatment, pathological subtypes, brain magnetic resonance imaging findings, epidermal growth factor receptor (EGFR) mutation details, anaplastic lymphoma kinase (ALK) rearrangement, PD-L1 expression, presence of extracranial metastases, neurological symptoms due to BM, and treatment history, were retrieved from electronic medical records. If multiple BMs were found, the largest lesion's diameter was recorded. The outcome variable was overall survival (OS), which was measured from the time of initial diagnosis of NSCLC with BM to the day of reported death due to any cause according to follow-up data. Patients who were lost to follow-up were excluded. Patients who were alive at the end of the study period were censored at that time.

Tumor tissue samples were obtained from either BM at the time of resection or lung nests by core-needle or excisional biopsy. All patients diagnosed with adenocarcinoma were examined for driver mutation status (EGFR and ALK) (SRL, Inc., Hachioji, Tokyo). All tissue samples were also immunohistochemically tested for PD-L1 expression (SRL, Inc., Hachioji, Tokyo). The proportion of tumor cells with positive membranous staining (tumor proportion score, TPS) was assessed (SRL, Inc., Hachioji, Tokyo). Positive PD-L1 expression was defined as staining in $\geq$50 % of the tumor cells.

The systemic treatment regimen was determined by the respiratory physician based on a comprehensive assessment of the individual patient's condition. The cohort was stratified according to the treatment regimen received as first-line therapy. Patients receiving immune checkpoint inhibitor (ICI) combined with platinum-doublet chemotherapy and patients receiving ICI monotherapy as first-line therapy were assigned to the ICI group. Patients receiving tyrosine kinase inhibitor (TKI) as first-line therapy were assigned to the TKI group. Patients receiving chemotherapy as first-line therapy were grouped into the chemotherapy group. All patients who received at least one treatment cycle were included.

### 2.3. Statistical analysis

To determine the differences between groups, chi-square or Fisher's exact test was performed for categorical covariates. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazard models were adopted to analyze the prognostic factors for OS. The results of the initial univariate analysis were used to determine which confounding variables were included in the multivariate analysis; any variable with $p < 0.05$ was included in the multivariate model.

Statistical significance was defined as $\alpha = 0.05$. All data were analyzed using the Statistical Package for the Social Sciences software version 23.0 (IBM, Armonk, NY).

## 3. Results

### 3.1. Patient characteristics

Among 53 consecutive patients with metastatic tumors with KPS of ≤70 and with NSCLC as the primary tumor, three were ineligible for aggressive treatment according to a respiratory physician, and were indicated for palliative treatment. The remaining 50 patients were included in this study. KPS at the initial presentation was 40–70, corresponding to ECOG-PS 2–3. Upfront intracranial treatment was given in 58 % of the patients and KPS after the intracranial treatment was 50–80. KPS at initial presentation was slightly lower in the ICI group compared with the other two groups, but its distribution was not significantly different among the three groups. Conversely, after upfront intracranial treatment, KPS was significantly better in the chemotherapy group (Table 1). Among all the patients, 16, 21, and 13 patients received systemic administration of TKIs, ICIs, and chemotherapy only, respectively (Fig. 1). TKIs were mainly considered as the first choice of treatment if patients had EGFR/ALK mutations. Patients with TPS ≥50 % were given ICIs.

In the ICI group, 7 patients received pembrolizumab monotherapy, and 14 received combination therapy of pembrolizumab with platinum plus pemetrexed followed by maintenance pembrolizumab alone. In patients with TPS <50 % and no driver mutation, only standard chemotherapy (platinum combined with pemetrexed) was performed. The entire cohort was followed up for an average of 22.5 months (standard deviation, ±18.9 months). The entire cohort's mean age was 67.1 years (standard deviation, ±8.5 years). No significant association was found between the treatment groups for baseline characteristics, such as age, sex, pathology, diameter of

**Table 1**
Patients' baseline characteristics.

| Patient characteristics | Total | Chemotherapy alone | ICIs | TKIs | P value |
|---|---|---|---|---|---|
| **Number of patients** | 50 (100 %) | 13 (26 %) | 21 (42 %) | 16 (32 %) | |
| **Age** | | | | | |
| <65 | 17 (34 %) | 3 (23 %) | 9 (43 %) | 5 (31 %) | 0.485 |
| 65–74 | 22 (44 %) | 5 (38 %) | 9 (43 %) | 8 (50 %) | |
| ≥75 | 11 (22 %) | 5 (38 %) | 3 (14 %) | 3 (19 %) | |
| **Sex** | | | | | |
| Male | 33 (66 %) | 9 (69 %) | 16 (76 %) | 8 (50 %) | 0.240 |
| Female | 17 (34 %) | 4 (31 %) | 5 (24 %) | 8 (50 %) | |
| **KPS at diagnosis** | | | | | |
| ≤40 | 4 (8 %) | 0 (0 %) | 2 (9.5 %) | 2 (12.5 %) | 0.291 |
| 50 | 11 (22 %) | 2 (15.4 %) | 7 (33.3 %) | 2 (12.5 %) | |
| 60–70 | 35 (70 %) | 11 (84.6 %) | 12 (57.1 %) | 12 (75 %) | |
| **KPS after intracranial local treatment** | | | | | |
| ≤50 | 1 (2 %) | 0 (0 %) | 0 (0 %) | 1 (6.25 %) | <0.001 |
| 60–70 | 34 (68 %) | 1 (7.7 %) | 19 (90.5 %) | 14 (87.5 %) | |
| ≥80 | 15 (30 %) | 12 (92.3 %) | 2 (9.5 %) | 1 (6.25 %) | |
| **Pathology** | | | | | |
| Adenocarcinoma | 44 (88 %) | 11 (85 %) | 17 (81 %) | 16 (100 %) | 0.191 |
| Squamous/large cell | 6 (12 %) | 2 (15 %) | 4 (19 %) | 0 (0 %) | |
| **Diameter of maximum brain metastasis (mm)** | | | | | |
| <10 | 21 (42 %) | 6 (46 %) | 6 (29 %) | 9 (56 %) | 0.329 |
| >10, <30 | 25 (50 %) | 7 (54 %) | 12 (57 %) | 6 (38 %) | |
| ≥30 | 4 (8 %) | 0 (0 %) | 3 (14 %) | 1 (6 %) | |
| **Number of BM** | | | | | |
| 1–4 | 28 (56 %) | 8 (62 %) | 12 (57 %) | 8 (50 %) | 0.819 |
| ≥5 | 22 (44 %) | 5 (38 %) | 9 (43 %) | 8 (50 %) | |
| **Extracranial metastasis** | | | | | |
| No | 23 (46 %) | 7 (54 %) | 9 (43 %) | 7 (44 %) | 0.911 |
| Yes | 27 (54 %) | 6 (46 %) | 12 (57 %) | 9 (56 %) | |
| **Symptomatic** | | | | | |
| No | 27 (54 %) | 7 (54 %) | 12 (57 %) | 8 (50 %) | 0.911 |
| Yes | 23 (46 %) | 6 (46 %) | 9 (43 %) | 8 (50 %) | |
| **Upfront intracranial treatment** | | | | | |
| No | 21 (42 %) | 8 (62 %) | 6 (29 %) | 7 (44 %) | 0.164 |
| Yes | 29 (58 %) | 5 (38 %) | 15 (71 %) | 9 (56 %) | |
| **TMN** | | | | | |
| T1-2 | 22 (44 %) | 4 (31 %) | 9 (43 %) | 9 (56 %) | 0.385 |
| T3-4 | 28 (56 %) | 9 (69 %) | 12 (57 %) | 7 (44 %) | |
| **TMN** | | | | | |
| N0 | 10 (20 %) | 2 (15 %) | 3 (14 %) | 5 (31 %) | 0.393 |
| N1-3 | 40 (80 %) | 11 (85 %) | 18 (86 %) | 11 (69 %) | |

Chi-square or Fisher's exact test was used for categorical covariates.

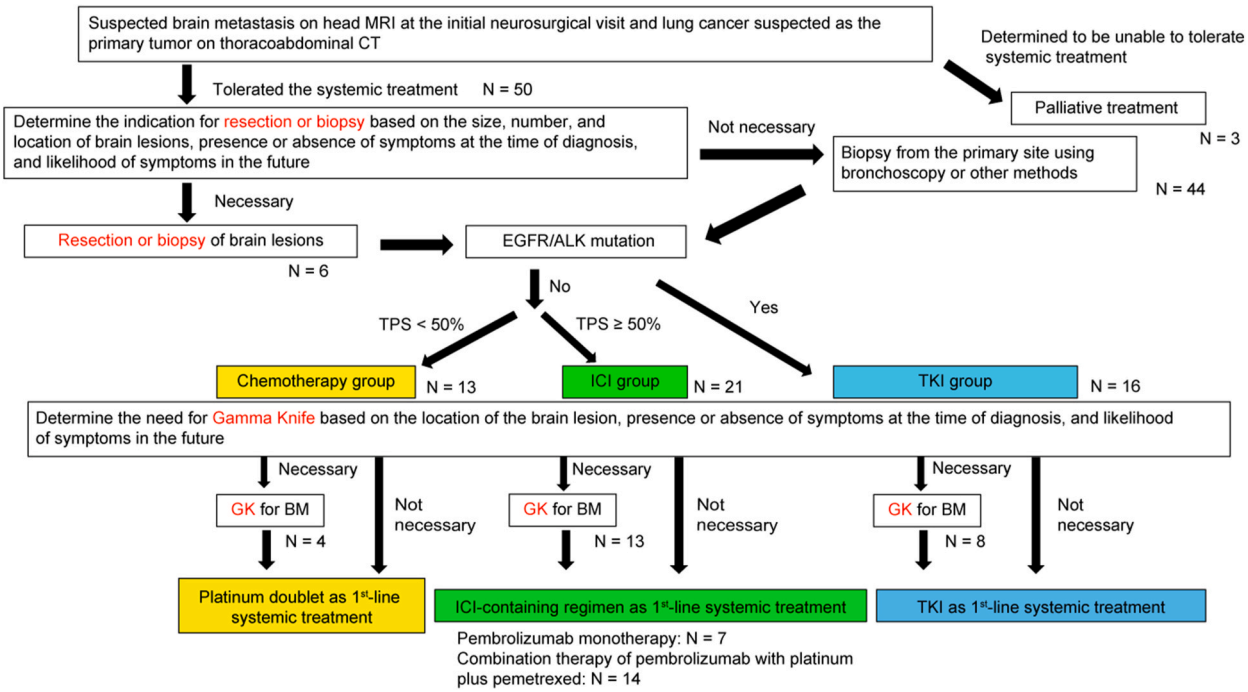


**Fig. 1.** Flow chart of the study patient selection. MRI: magnetic resonance imaging, EGFR/ALK: epidermal growth factor receptor/anaplastic lymphoma kinase, ICI: immune checkpoint inhibitor; TKI: tyrosine kinase inhibitor, GK: Gamma knife, TPS: tumor proportion score.

the largest BM, number of BM, symptoms due to BM, and rate of upfront intracranial treatment. The factor showing significant differences among the three groups was KPS after intracranial treatment, with most of the chemotherapy group achieving a KPS of ≥80, whereas the majority of the remaining two groups had a KPS of 60–70 (Table 1).

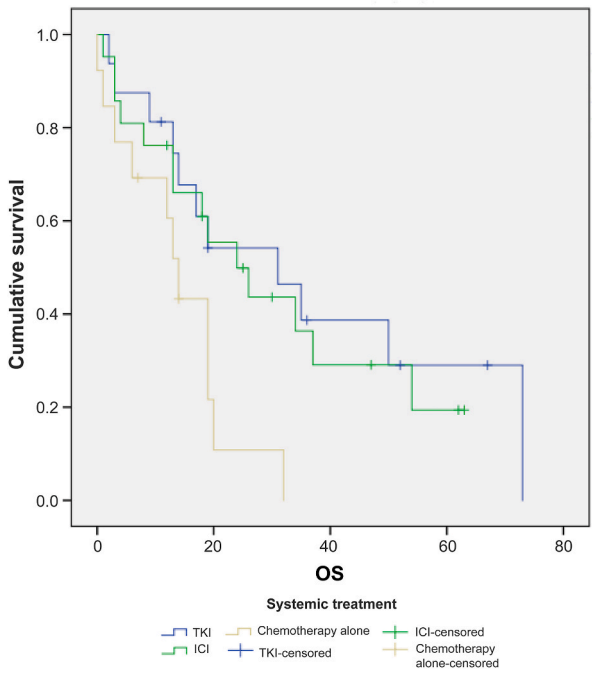


**Fig. 2.** Overall survival (OS) from the time of diagnosis of nonsmall cell lung cancer (NSCLC) among patients stratified by systemic treatment method.

### 3.2. OS

The entire cohort's median survival duration was 18 months (95 % confidence interval [CI], 1.5–62.6). The median survival times for the TKI, ICI, and chemotherapy alone groups were 19 (95 % CI, 2.8–68.5), 19 (95 % CI, 3.0–62.0), and 13 (95 % CI, 1.2–24.8), respectively. The survival time for the chemotherapy alone group was significantly shorter than that of the other two groups ($p = 0.046$, TKI vs. chemotherapy; $p = 0.022$, ICI vs. chemotherapy; $p = 0.024$, ICI vs. TKI; $p = 0.698$) (Fig. 2). Herein, the ICI group included two different regimens: pembrolizumab monotherapy and platinum combination therapy in 7 and 14 cases, with a median survival of 19 (95 % CI, 1.6–58.2) and 21.5 (95 % CI, 3.7–56.8) months, respectively. Both groups with different regimens showed a trend toward longer survival compared with the group receiving standard chemotherapy alone at 13 months (95 % CI, 1.2–24.8); however, no statistically significant difference was observed ($p = 0.900$, ICI monotherapy vs chemotherapy; $p = 0.219$, ICI combined therapy vs chemotherapy).

### 3.3. Analysis of survival

In the univariate analysis, age, KPS, pathology, diameter of the largest BM, extracranial metastasis, symptoms due to BM, and number of brain metastases did not impact survival (Table 2). Sex and type of systemic treatment (chemotherapy) were the only

**Table 2**
Univariate (log-rank) and multivariate (Cox proportional HR test) analyses for overall survival.

| Factor | Univariate | Multivariate | |
|---|---|---|---|
| | p value | HR (95 % CI) | p value |
| **Age** | | | |
| −69 | | | |
| 70- | 0.247 | | |
| **Sex** | | | |
| Female | | | |
| Male | **0.042** | 0.53 (0.25–1.14) | 0.102 |
| **KPS at diagnosis** | | | |
| <70 | | | |
| 70–80 | | | |
| 90–100 | 0.488 | | |
| **KPS after intracranial local treatment** | | | |
| <70 | | | |
| 70–80 | 0.406 | | |
| 90–100 | | | |
| **Pathology** | | | |
| Adenocarcinoma | | | |
| Squamous | 0.919 | | |
| **Diameter of maximum brain metastasis (mm)** | | | |
| <10 | | | |
| >10, <30 | 0.577 | | |
| ≥30 | | | |
| **Number of BM** | | | |
| 1–4 | | | |
| ≥5 | 0.074 | | |
| **Extracranial metastasis** | | | |
| No | | | |
| Yes | 0.112 | | |
| **Symptomatic BM** | | | |
| No | | | |
| Yes | 0.481 | | |
| **TKI(EGFR-/ALK-) therapy** | | | |
| No | | | |
| Yes | 0.233 | | |
| **Immunotherapy** | | | |
| No | | | |
| Yes | 0.479 | | |
| **Chemotherapy alone** | | | |
| No | | | |
| Yes | **0.009** | 0.44 (0.20–0.94) | 0.034 |
| **TMN** | | | |
| T1-2 | | | |
| T3-4 | 0.093 | | |
| **TMN** | | | |
| N0 | | | |
| N1-3 | 0.124 | | |

Any variable with $p < 0.05$ was included in the multivariate model along with systemic treatment.

predictors of OS identified in the univariate analysis, and these two factors were included in the multivariate analysis. Chemotherapy alone for systemic treatment [p = 0.034; HR, 0.44 (95 % CI: 0.20–0.94)] remained a significant factor in predicting OS on the multivariate analysis.

## 4. Discussion

With advances in systemic therapy, survival can be prolonged in patients stage IV NSCLC with distant metastases. Systemic treatment (cytotoxic anticancer drugs, TKIs, ICIs) prolongs OS compared with palliative treatment, primarily for patients with stage IV NSCLC with PS 0–1 [20]. Reportedly, systemic chemotherapy improves OS in patients with NSCLC and BM. For patients with stage IV NSCLC, monotherapy with third-generation cytotoxic anticancer drugs improved 1-year survival by approximately 7 % compared with palliative treatment [21]. Further prolongation of OS was reported with the combination of platinum and third-generation cytotoxic anticancer drugs [22]. On the contrary, a 1.26 % treatment-related death due to myelosuppression, cardiovascular toxicity, and pulmonary toxicity was reported [23] and treatment of patients with poor PS is not recommended. Further, ICI has been effective in patients with NSCLC, BM, and good PS, contributing to prolonged survival; however, at present, there is no evidence of a benefit or safety of immunotherapy for patients with PS 3–4, whereas patients with poor PS and active BM should avoid immunotherapy [24–26]. There is no evidence of a direct effect on intracranial lesions, and conversely, this may limit BM treatment [27]. Meanwhile, molecular-targeted therapies for patients with EGFR mutations and ALK gene rearrangements can effectively control systemic disease, including BM, which are generally less toxic than cytotoxic anticancer drugs and contribute to further prolonged survival [6]. Additionally, these drugs are recommended for patients with poor PS and BM. Thus, systemic treatment other than TKIs is currently not recommended for patients with active BM or poor PS as they do not benefit from their survival-prolonging effects.

The presence of BM and poor PS is considered poor prognostic factors for survival among patients with NSCLC. In addition to respiratory impairment, the PS of patients with NSCLC deteriorates because of impaired consciousness, movement, nutrition, and physical fitness. Impaired consciousness may also be caused by metastases to brain regions involved in arousal, increased intracranial pressure resulting from BM, and meningeal dissemination. BM to the motor cortex and circuits directly causes motor disturbances. Moreover, cognitive dysfunction resulting from BM contributes to systemic symptoms as a cause of reduced activity during daily life (ADL), physical fitness, and anorexia. Thus, BM can deteriorate PS for all aspects and hinder the prospect of systemic treatment [28,29].

Lung Cancer Molecular Markers Graded Prognostic Assessment (Lung molGPA) [30], a representative prognostic scale for survival time in NSCLC patients, uses five independent prognostic factors including KPS and number of BM. The Lung molGPA predicts a median survival time for patients with adenocarcinoma with poor PS and BM to be 6.9–26.5 months and 6.9–13.7 months with and without driver mutations, respectively. All patients in this study had BM, with an initial KPS of 40–70, which corresponds to poor PS. The median OS in the TKI group was 19 months (95 % CI, 2.8–68.5), that was almost the same as that predicted for the Lung molGPA. In contrast, the median OS in the ICI group and chemotherapy alone group where driver mutations were absent, was 19 months (95 % CI, 3.0–62.0) and 13 months (95 % CI, 1.2–24.8), respectively. The median OS in the chemotherapy alone and TKI groups was similar to that predicted by Lung molGPA, whereas the median OS in the ICI group was longer compared with that predicted by Lung molGPA and similar to that in the TKI treatment group. This indicates that ICI treatment was more effective in the study population with BM and poor PS at initial presentation compared with that of previous studies. Herein, the intracranial treatment was planned with a similar policy of “avoiding ADL reduction due to intracranial lesions” in all three groups. However, as mentioned, no OS prolongation was achieved in chemotherapy alone or TKI groups, and only the median OS in the ICI group was prolonged. This may have occurred because intracranial treatment was not the only contributing factor to OS prolongation, whereas the ICI treatment was inherently more effective because of the appropriate intracranial treatment planning. Our results indicate that there is a subgroup of patients for whom immunotherapy is effective, as PS improves with individualized intracranial treatment in the patient population unsuitable for immunotherapy. Therefore, although the present treatment is not effective in all patients with poor PS, there is a subgroup of patients with poor PS for whom immunotherapy is effective, and patients with BM at initial presentation are candidates for this subgroup.

A unique feature of the cohort included in this study was that in >50 % of the patients, the primary cause of poor PS at initial visit was symptomatic BM, and upfront intracranial treatment resulted in improvement of neurological abnormalities, with performance status improving to PS2 or lower in almost all patients before systemic treatment. In patients with BM, PS can vary greatly depending not only on the lesion size and number, but also on the lesion location, treatment choice, and timing, leading to a change in treatment strategy and a significant reduction in survival time. Management of intracranial lesions is therefore important. However, studies examining the intracranial effects of systemic therapy are often limited to asymptomatic or nonactive lesions only, and studies of symptomatic or active BM are limited [25,31–36]. Many patients with poor PS have active BM [35,36], and recent reports have been inconclusive as to whether the two independently correlate with survival. With advances in intracranial and systemic therapies, the number of patients undergoing aggressive intracranial therapy has increased in recent years. This increase has led to scattered reports indicating that the presence of BM is not a poor prognostic factor for survival [36–39]. In a previous retrospective study, the number of BMs was not correlated to survival time in patients with lung cancer who underwent intracranial local therapy, but both KPS and systemic therapy after BM treatment were correlated with survival time [35]. The JLGK0901 trial showed that the OS of patients with 5–10 BMs was not inferior to that of patients with 2–4 BMs if they received stereotactic radiosurgery (SRS) [40]. Nieder et al. also reported prolonged survival when local brain-directed approaches were added to systemic therapy in patients with BM at the time of initial presentation [36]. Waqar et al. also reported that the addition of intracranial local therapy, including surgery or SRS, prolonged OS only in patients with BM at the first presentation [14]. Thus, most studies reporting that the presence of BM was not correlated with survival time had appropriate upfront intracranial treatment, followed by effective systemic therapy [41]. Patients whose PS can be

expected to improve with upfront intracranial local treatment, as in the present study, may be a subpopulation that would benefit from systemic treatment, even if they have poor PS at the initial visit.

Recently, immunotherapy has greatly advanced the treatment of NSCLC with BM, significantly prolonging OS in patients with PS0-1 compared with standard chemotherapy. A pooled analysis of KEYNOTE-021, −189, and −407 showed a median OS of 18.8 months for patients with PS0-1 and BM [31]. PePS2, which examined the benefit and safety of pembrolizumab treatment in patients with PS2, reported a median OS of 7.9 (2.6–not reported [NR]) months for patients using pembrolizumab as first-line therapy and 14.6 (4.6–NR) months for patients with TPS ≥50 % [18]. While the PePS2 results barely support immunotherapy for PS2, there is currently no evidence of benefit or safety of active treatment for PS3-4 patients. Thus, it is believed that patients with poor PS and active BM should avoid immunotherapy [24–26]. The reason for previous studies reporting very short survival in poor PS patients receiving immunotherapy is assumed to be the limited number of studies and the lack of classification of the diversity of the poor PS population. Recently, attempts have been made to select a population among poor PS for whom immunotherapy is effective. A previous prognostic study involving 128 NSCLC patients with PS2 reported a significant effect of immunotherapy, with >70 % of patients surviving at 21 months in a subgroup where neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and pretreatment of steroid met certain criteria [19]. Several studies that have successfully classified this diverse population have reported long-term survival comparable to that of the present study [16,19].

Herein, the immunotherapy group included two regimens: pembrolizumab monotherapy and combination therapy of pembrolizumab with a platinum-doublet. Combination therapy using pembrolizumab and a platinum-doublet is administered for the initial course, with pembrolizumab alone as maintenance therapy. Combination therapy is considered more effective than ICI alone, as chemotherapy enhances the T-cell response and suppresses tumor-activated macrophages; however, whether efficacy outweighs safety for combination therapy in patients with BM and PS 2 or higher is yet to be determined. For patients with ECOG-PS 0–1, KEYNOTE-024 and -042 indicated that pembrolizumab monotherapy considerably prolongs OS compared with platinum-based combination therapy [33]. No large studies have compared the survival benefit of pembrolizumab monotherapy with that of platinum-based combination therapy in patients with NSCLC and BM. Pooled analyses of KEYNOTE-021, -189, and −407 revealed that pembrolizumab combination therapy was associated with a better objective response rate and PFS compared with chemotherapy in PS0-1 patients with BM [31]; however, the superiority of a immunotherapy regimen (pembrolizumab alone or in combination with chemotherapy) among the two concerning prolonged survival for patients with poor PS and BM is unclear.

Herein, the ICI group included two different regimens: pembrolizumab monotherapy and platinum combination therapy in 7 and 14 cases, with a median survival of 19 (95 % CI, 1.6–58.2) and 21.5 (95 % CI, 3.7–56.8) months, respectively. Both groups with different regimens showed a trend toward longer survival compared with the group receiving standard chemotherapy alone at 13 months (95 % CI, 1.2–24.8); however, no statistically significant difference was observed ($p = 0.900$, ICI monotherapy vs chemotherapy; $p = 0.219$, ICI combined therapy vs chemotherapy). The lack of significant differences in survival for both ICI regimens compared with the standard chemotherapy group was because of insufficient patient numbers. This should not affect the reliability of the comparison of treatment efficacy between ICIs and chemotherapy. It is yet to be determined which of the two regimens is more appropriate for prolonging survival for the patient group.

Intracranial treatment in patients with immunotherapy requires consideration of issues, such as treatment timing and steroid administration, which are the key to PS maintenance. Some clinical trials target untreated or progressive asymptomatic BM ≥ 2 cm diameter; however, those in the eloquent area are treated with stereotactic radiotherapy (SRS) or other therapies before enrolment. Thus, immunotherapy for patients with NSCLC and BM is considered inferior to standard chemotherapy and TKIs concerning direct therapeutic effect on intracranial lesions in the short term post administration [18], and additional local treatment is considered necessary for symptomatic or active BM. In addition, several factors reportedly influence the efficacy of immunotherapy and affect patient survival. First, the greatest impact on the BM treatment is the limited timing of steroid use. In patients with advanced NSCLC receiving frontline pembrolizumab monotherapy, any use of steroids before or during treatment was reportedly associated with an 86 % increase in the risk of progression and a 2.3-fold increase in the risk of death [42]. In the current study, steroids were not used before or after intracranial treatment for patients scheduled to receive ICI. Gamma knife (GK) treatment was performed for lesions near the eloquent area, even if these lesions were asymptomatic. Additionally, the intracranial treatment plan was tailored to individual intracranial conditions, including excision of lesions with a size that would cause severe edema if GK were performed. This retrospective study did not have a uniform protocol for intracranial treatment because the tailor-made treatment considered optimal for each patient was planned based on the intracranial lesion and subsequent systemic treatment with each patient in mind. However, individual intracranial therapies are not unique and are a standard practice in all centers. Moreover, establishing a unified treatment flow for the selection and timing of each treatment as a treatment plan can potentially be formulated by the neurologists involved in cancer treatment and is based on preventing ADL deterioration resulting from intracranial lesions. In the future, conducting a prospective study with a unified protocol for intracranial treatment may be necessary.

In our study, none of the Lung molGPA prognostic factors was significantly correlated to OS. KPS was found to be correlated with OS in many previous reports [35,36,43], with most of them having patients with KPS of 60–70. Jünger et al. reported that KPS ≥70 post-BM-treatment was significantly correlated with prolonged survival. Nieder et al. examined the prognostic factors for prolonged survival in patients with BM at the first presentation in a variety of primary cancer types and reported that KPS <60 is a poor outcome factor [36]. Dinglin et al. showed that KPS <60 is significantly correlated with survival outcome [43]. As these previous studies have shown, KPS 60–70 or PS2 is a clear borderline with respect to correlation with OS, and all patients in this study were above borderline after upfront intracranial treatment. This may be one reason why KPS was not considered a significant factor in the univariate analysis. Since all patients with driver mutations received TKIs, the gene status of Lung molGPA corresponds to the TKI in this study. In the present study, among patients without driver mutation, those receiving ICIs showed the same OS prolongation effect as those in the

driver mutation group, suggesting that the survival benefit of TKIs is no longer significant. The prognostic factors of Lung mol GPA, age, and extracranial metastasis were also not significantly correlated with OS in this study, which may be due to the small number of patients included in this study.

### *4.1. Limitations*

Our study had several limitations. First, the number of patients was small, which may have led to statistically nonsignificant results in terms of survival for some factors. Second, this was a single-center retrospective study of patients who visited a neurosurgery department during their first visit. Herein, we compared the survival of patients with BM at initial presentation via systemic treatment, aiming to optimizing systemic treatment by minimizing the decline in ADL caused by BM. In particular, patients treated with immunotherapy as systemic treatment may have benefited from an individualized intracranial treatment plan, including early intracranial intervention to refrain from steroid use during systemic treatment, even if they were asymptomatic at the first visit. Thus, selecting cases in which a neurologist was involved from the beginning to plan the intracranial treatment to minimize the ADL decline caused by BM was necessary. In general, selecting patients for neurosurgery may result in several patients with neurological symptoms but no symptoms in other body parts. Patients with neurosurgical consultation during their initial visit may have improved PS after the intracranial treatment. Thus, this may have led to a bias in the selection of patients. Third, the immunotherapy group included two different schemes: patients treated with pembrolizumab monotherapy and combined chemotherapy, so the impact of chemotherapy cannot be excluded. Finally, there was no unified regimen for intracranial therapies. Particularly in SRS, prior treatment was given not only to symptomatic lesions but also to asymptomatic lesions close to the eloquent area. Despite these limitations, the TKI and ICI groups showed longer survival than patients who received chemotherapy alone as systemic therapy. This may indicate that even in BM and poor PS population, which were considered difficult cases to benefit from ICI treatment, patients who could benefit from intracranial pretreatment may be candidates for ICI.

## 5. Conclusions

In patients with poor PS and BM at the initial diagnosis of NSCLC, relatively good outcomes were achieved when treatment tailored to the site and symptoms of individual BM lesions was given prior to systemic treatment. Systemic treatment was significantly correlated with survival. Moreover, survival in the immunotherapy group was comparable to that in the TKI group. Our patient population was a good indication for immunotherapy despite their poor PS at the initial presentation. The results indicate that using site- and size-specific treatments of BM can expand the immunotherapy indications and maximize its efficacy in populations with a potential improvement in PS. Intracranial tailor-made treatment was primarily effective in immunotherapy in which steroid administration was avoided, and it is potentially effective with other systemic therapies. Personalized treatment of intracranial lesions will potentially lead to improved systemic status, thereby giving patients the opportunity to receive effective systemic treatment.

## Glossary

None.

## Ethical approval

This study was approved by the institutional ethics review board at the National Hospital Organization Disaster Medical Center (approval number 2019-3).

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## Data availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

## Declaration of generative AI in scientific writing

Not applicable.

## CRediT authorship contribution statement

**Kyoko Sumiyoshi:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Hiroshi Yatsushige:** Resources. **Keigo Shigeta:** Resources. **Yuuki Aizawa:** Resources. **Asuka Fujino:** Resources. **Nozomi Ishijima:** Resources. **Takanori Hayakawa:** Supervision, Resources.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38128.

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