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RESEARCH PAPER

Prognostic impact of *EGFR*/*ALK* alterations in leptomeningeal metastasis from lung adenocarcinoma treated with whole-brain radiotherapy

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Abstract

The prognosis and prognostic factors of patients receiving whole-brain radiotherapy (WBRT) for leptomeningeal metastasis (LM) from lung adenocarcinoma have not been established. Particularly, the impact of *EGFR* mutations and *ALK* rearrangements on survival remains unclear. This retrospective study evaluated the prognosis and prognostic factors of patients receiving WBRT for LM. We evaluated overall survival (OS) from WBRT initiation and clinical variables in 80 consecutive patients receiving WBRT for LM from lung adenocarcinoma at our institution between June 2013 and June 2021. After a median follow-up of 5.2 (range 0.5–56.5) months, the median OS was 6.2 months (95% CI 4.4–12.4). Of the 80 patients, 51 were classified as *EGFR/ALK* mutant (*EGFR*: 44; *ALK*: 6; both: 1) and 29 as wild-type. The median OS was 10.4 (95% CI 5.9–20.9) versus 3.8 (95% CI 2.5–7.7) months in the *EGFR/ALK*-mutant versus wild-type patients (HR = 0.49, $P = 0.0063$). Multivariate analysis indicated that *EGFR/ALK* alterations (HR = 0.54, $P = 0.021$) and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 (HR = 0.25, $P < 0.001$) were independent factors associated with favorable OS. Among the patients who underwent brain MRI before and after WBRT, intracranial progression-free survival was longer in the 26 *EGFR/ALK*-mutant than 13 wild-type patients (HR = 0.31, $P = 0.0039$). Although the prognosis of patients receiving WBRT for LM remains poor, *EGFR/ALK* alterations and good ECOG PS may positively impact OS in those eligible for WBRT.

Keywords Leptomeningeal metastasis · Whole brain radiotherapy · Lung adenocarcinoma · *EGFR* · *ALK*

Abbreviations

ALK	Anaplastic lymphoma kinase
CSF	Cerebrospinal fluid
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
LANO	Leptomeningeal Assessment in Neuro-Oncology
LM	Leptomeningeal metastasis
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
TKI	Tyrosine kinase inhibitor
WBRT	Whole-brain radiotherapy

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Background

Leptomeningeal metastasis (LM) derived from lung adenocarcinoma is a fatal condition associated with a poor prognosis. The incidence of LM has been increasing, especially

in patients with *EGFR*-mutant or *ALK*-rearranged lung adenocarcinoma, as a result of prognostic improvements due to recent developments in molecular targeted therapies [1]. Although molecular targeted therapies with better blood–brain barrier penetration improve the prognosis of patients with LM derived from *EGFR*-mutant or *ALK*-rearranged (*EGFR*/*ALK*-mutant) lung adenocarcinoma, there are still few treatment options for LM, especially after failing molecular targeted therapies [2].

Whole-brain radiotherapy (WBRT) is a treatment option for patients with LM derived from lung adenocarcinoma [3, 4]. WBRT is useful for palliating symptoms, improving cerebrospinal fluid (CSF) flow, and debulking tumors [2]. On the other hand, several studies reported that WBRT does not improve survival, suggesting the possibility of omitting WBRT [5, 6]. The US National Comprehensive Cancer Network recommends WBRT as a treatment option for LM originating from solid tumors, especially in patients with the following factors: acceptable performance status, no major neurological deficits, minimal systemic disease, and reasonable systemic treatment options [4].

However, these WBRT indications may not apply to non-small cell lung cancer (NSCLC) patients because actionable gene alterations such as *EGFR*/*ALK* alterations can affect survival outcomes [3]. This suggests that the prognosis after treatment, including WBRT, for LM originating from *EGFR/ALK*-mutant NSCLC may differ from that for LM originating from other cancers. Furthermore, identifying favorable prognostic factors after WBRT would enable stratification of LM patients and selection of appropriate treatments [4]. Nevertheless, the prognosis and prognostic factors of patients with lung adenocarcinoma who receive WBRT for LM have not been established. In particular, the impact of *EGFR* mutations or *ALK* rearrangements on survival remains unclear.

We conducted this retrospective study to evaluate the prognosis of patients after receiving WBRT for LM derived from lung adenocarcinoma, focusing on the impact of *EGFR*/*ALK* status on OS after WBRT initiation.

Methods

Patients

We retrospectively evaluated 80 consecutive patients who received WBRT for LM from lung adenocarcinoma at our institution between June 2013 and June 2021. The *EGFR* status of all patients was examined by PCR, and the presence of *ALK* rearrangements was examined by immunohistochemistry, fluorescence in situ hybridization, and PCR. LM was diagnosed by contrast-enhanced brain magnetic resonance imaging (MRI) in 77 patients (96%) [7] and by contrast-enhanced computed tomography (2 patients) and CSF cytology (1 patient) in the remaining 3 patients.

To determine whether the presence of *EGFR/ALK* alterations is a prognostic factor after WBRT, we divided the patients according to their *EGFR/ALK* status into the following two groups: the *EGFR/ALK*-mutant group, defined as patients with lung adenocarcinoma harboring *EGFR* mutations and/or *ALK* rearrangements, and the wild-type group, defined as those with neither *EGFR* nor *ALK* alterations. This retrospective study was approved by the National Cancer Center Hospital East Institutional Review Board (Protocol Number 2017-440).

Radiotherapy

All patients received WBRT using three-dimensional conformal radiotherapy. The dose fractionation of WBRT was 30 Gy in 10 fractions before the COVID-19 outbreak. Since May 2020, WBRT at 20 Gy in 5 fractions was applied according to the National Comprehensive Cancer Network guidelines [4]. No patient received intensity-modulated radiotherapy. An additional boost, including the simultaneous integrated boost technique, was not administered. We defined the clinical target volume as the entire intracranial CSF and whole brain, which included all gross tumors because the radiographic findings of LM are unclear. The planning target volume was generated by adding a circumferential margin of at least 5 mm to the clinical target volume. The inferior border of the radiation field was at the lower edge of the C1 or C2 vertebra. We used 6–10 MV photon beams. No patient received craniospinal irradiation.

Intracranial response evaluation

We evaluated the intracranial response in patients who underwent contrast-enhanced brain MRI both before and after WBRT using the Leptomeningeal Assessment in Neuro-Oncology (LANO) scale [8]. The following LM-related MRI findings were assessed: subarachnoid or ventricular nodules, leptomeningeal enhancement, hydrocephalus, and Evan's index. We defined nodules within 2 mm from the brain surface as LM based on the LANO scale. The other nodules were regarded as brain metastases.

Statistical analysis

We compared categorical variables using Fisher's exact test and continuous variables using the Wilcoxon rank sum test. Overall survival (OS) was calculated from the date of WBRT initiation until death. Intracranial progression-free survival (PFS) was calculated from the date of WBRT initiation until death or progressive intracranial disease based on the LANO scale. Follow-up was censored on June 2022.

We analyzed the following variables at WBRT initiation as potential factors associated with OS and intracranial PFS: age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), *EGFR/ALK* status, presence of brain metastasis, presence of hydrocephalus, presence of extracranial metastasis, primary tumor control, and number of systemic chemotherapy regimens [including central nervous system-penetrant *EGFR* and *ALK* tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors] before WBRT. OS and intracranial PFS were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. We performed Cox multivariate analysis of the factors significantly associated with OS in the Cox univariate analyses. The cumulative incidence of intracranial failure was calculated using Gray's test. All tests were two-sided, and *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R version 4.1.1.

Results

Patient characteristics

Among the 80 patients, 75 (94%) completed WBRT, whereas the remaining discontinued WBRT because of clinical deterioration (WBRT dose range 3–18 Gy). The dose fractionation of WBRT was 30 Gy in 10 fractions in 72 patients and 20 Gy in 5 fractions in 8 patients. Fifty-nine patients (74%) received steroids concurrently with WBRT. The median follow-up time of all patients was 5.2 (range 0.5–56.5) months from the date of WBRT initiation. Of the 80 patients, 51 were assigned to the *EGFR/ALK*-mutant group (*EGFR* mutations were found in 44 patients, *ALK* rearrangements in 6, and both *EGFR* and *ALK* alterations in 1) and 29 to the wild-type group. The *EGFR* mutations comprised the exon 21 L858R mutation (n = 23), exon 19 deletion (n = 18), exon 18 G719X mutation (n = 2), exon 21 L861Q mutation (n = 1), and exon 20 S768I mutation (n = 1).

The patient characteristics at WBRT initiation are shown in Table 1. The proportions of females ($P = 0.035$), patients with brain metastases ($P = 0.026$), and patients with extracranial metastases ($P = 0.012$) were significantly higher in the *EGFR/ALK*-mutant group than in the wild-type group. The *EGFR/ALK*-mutant group tended to receive more systemic chemotherapy regimens before WBRT compared with the wild-type group ($P = 0.091$). Notably, almost all patients in the *EGFR/ALK*-mutant group (n = 49, 96%) had failed at least one TKI before WBRT, resulting in disease progression to LM. These 49 patients had received a total of 72 *EGFR/ALK*-TKI related regimens before WBRT, as follows: gefitinib (n = 27), osimertinib (n = 14), erlotinib (n = 10), afatinib (n = 10), crizotinib (n = 5), alectinib (n = 4), and ceritinib (n = 2). Of the 49 patients, 22 continued TKIs beyond progressive disease at WBRT initiation, all showing LM-only progression.

Table 1 Patient characteristics at the initiation of WBRT for LM

Characteristic	*EGFR/ALK*-mutant (n = 51)	*EGFR/ALK* wild-type (n = 29)	*P*-value[b]
Age (years)[a]	63 (55–71)	67 (60–71)	0.52
Sex			0.035
Female	25 (49%)	7 (24%)	
Male	26 (51%)	22 (76%)	
ECOG PS			> 0.99
0–1	35 (69%)	20 (69%)	
2–3	16 (31%)	9 (31%)	
Brain metastases			0.026
Present	22 (43%)	5 (17%)	
Absent	29 (57%)	24 (83%)	
Hydrocephalus			0.36
Present	7 (14%)	7 (24%)	
Absent	44 (86%)	22 (76%)	
Extracranial metastases			0.012
Present	44 (86%)	17 (59%)	
Absent	7 (14%)	12 (41%)	
Primary control			0.63
Controlled	16 (31%)	11 (38%)	
Not controlled	35 (69%)	18 (62%)	
No. of prior systemic chemotherapy regimens			0.091
0	2 (4%)	4 (14%)	
1	15 (29%)	12 (41%)	
≥ 2	34 (67%)	13 (45%)	

ECOG PS Eastern Cooperative Oncology Group performance status

[a]Median (interquartile range)

[b]Wilcoxon rank sum test or Fisher's exact test

Relationship between OS and *EGFR/ALK* status in patients receiving WBRT for LM

Of the 80 patients, 61 (76%) died of disease progression. The median OS duration of all patients was 6.2 months (95% CI 4.4–12.4). OS was significantly longer in the *EGFR/ALK*-mutant group than in the wild-type group (median 10.4 [95% CI 5.9 to − 20.9] vs. 3.8 [95% CI 2.5–7.7] months; hazard ratio (HR) = 0.49 [95% CI 0.29–0.83]; $P = 0.0063$; Fig. 1). Among the clinical variables at WBRT initiation, an ECOG PS of 0–1 (HR = 0.22 [95% CI 0.12–0.40], $P < 0.001$) and controlled primary tumor (HR = 0.55 [95% CI 0.32–0.95], $P = 0.034$) were significantly associated with better OS in the univariate analyses. Multivariate analysis indicated that *EGFR/ALK* alterations (HR = 0.54 [95% CI 0.32–0.91],

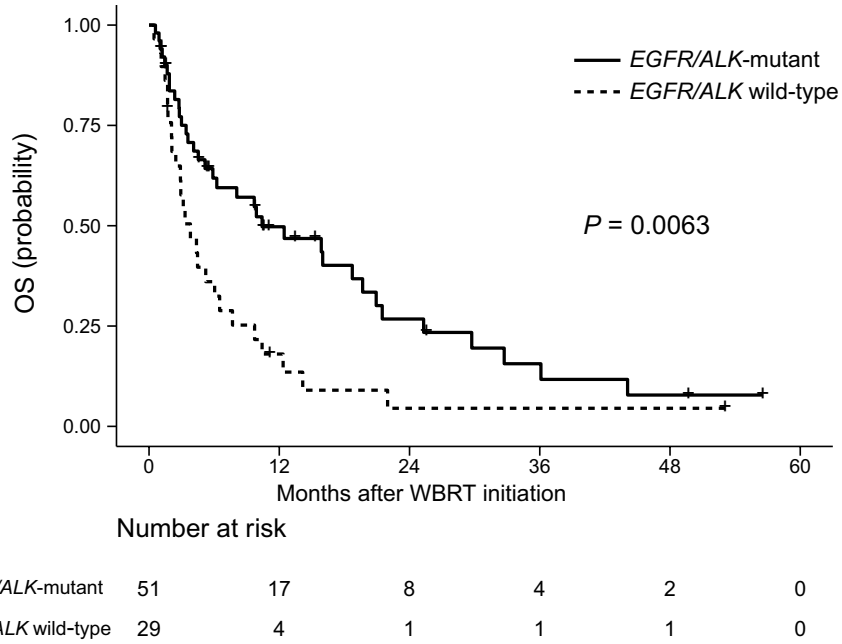

Fig. 1 Overall survival of patients receiving WBRT for leptomeningeal metastasis according to *EGFR/ALK* alteration status (n = 80). *OS* overall survival, *WBRT* whole-brain radiotherapy

$P = 0.021$) and an ECOG PS of 0–1 (HR = 0.25 [95% CI 0.32–0.95], $P < 0.001$) were independent factors associated with favorable OS after starting WBRT (Table 2). Among the *EGFR/ALK*-mutant patients, no significant difference was observed in OS between patients with *EGFR*-mutant and those with *ALK*-rearranged lung adenocarcinoma ($P = 0.76$; Supplementary Fig. 1).

The number of patients who received systemic chemotherapy after WBRT was significantly higher in the *EGFR/ALK*-mutant group than in the wild-type group (n = 43 [84%] vs. 12 [41%] patients, $P < 0.001$). The details of the systemic chemotherapy regimens after WBRT are shown in Supplementary Table 1. Of the 43 *EGFR/ALK*-mutant patients who received systemic chemotherapy, 41 received at least one subsequent *EGFR/ALK*-TKI after WBRT. Although most *EGFR/ALK*-mutant patients had failed at least one *EGFR/ALK*-TKI therapy before WBRT, *EGFR/ALK* alterations had a positive impact on OS in patients receiving WBRT for LM.

Intracranial PFS in patients undergoing brain MRI before and after WBRT

We evaluated the intracranial PFS of 39 patients who underwent brain contrast-enhanced MRI before and after WBRT. Of these, 18 patients (46%) experienced intracranial disease progression. The median intracranial PFS was 9.7 months (95% CI 6.5–15.7). Of the 39 patients, 26 (67%) had *EGFR/*

Table 2 Univariate and multivariate analyses of OS (n = 80)

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value[a]	HR	95% CI	*P*-value[b]
Age (≥ 70 vs. < 70 years)	1.44	0.79–2.64	0.23			
Sex (male vs. female)	1.39	0.82–2.35	0.22			
ECOG PS (0–1 vs. 2–3)	0.22	0.12–0.40	< 0.001	0.25	0.14–0.45	< 0.001
Brain metastases (present vs. absent)	0.77	0.44–1.34	0.36			
Hydrocephalus (present vs. absent)	1.08	0.55–2.15	0.82			
Extracranial metastases (present vs. absent)	1.63	0.88–3.02	0.11			
Primary control (controlled vs. not controlled)	0.55	0.32–0.95	0.034	0.59	0.34–1.03	0.064
No. of prior systemic chemotherapy regimens (≥ 2 vs. < 2)	1.54	0.91–2.59	0.10			
EGFR/ALK status (mutant vs. wild-type)	0.49	0.29–0.83	0.0063	0.54	0.32–0.91	0.021

[a] *P*-values were calculated using the log-rank test

[b] *P*-values were calculated using Cox univariate analysis

HR hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status

ALK alterations (22 with *EGFR* mutations, 3 with *ALK* rearrangements, 1 with both alterations). The frequencies of an ECOG PS of 0–1 ($P < 0.001$), a controlled primary tumor ($P = 0.0089$), and receiving fewer systemic chemotherapy regimens before WBRT ($P = 0.030$) were significantly higher in patients who were evaluated for intracranial PFS than in those who were not (Supplementary Table 2), implying that brain MRI can be performed in patients with a favorable background. Indeed, the median OS was longer (12.4 months, 95% CI 9.7 to − 21.5) in the patients who were evaluated for intracranial PFS compared with all 80 patients (6.2 months, 95% CI 4.4–12.4).

The median intracranial PFS was 12.5 (95% CI 8.1–21.5) and 6.1 (95% CI 3.8–not reached) months in the *EGFR/ALK*-mutant and wild-type groups, respectively (HR = 0.31 [95% CI 0.14–0.72], $P = 0.0039$; Fig. 2). Among the evaluated variables at WBRT initiation, the presence of *EGFR/ALK* alterations was the only prognostic factor associated with favorable intracranial PFS (Table 3). Considering death as a competing risk, the cumulative incidences of intracranial failure at 6 and 12 months were moderately lower in the *EGFR/ALK*-mutant group (15% and 24%, respectively) than in the *EGFR/ALK* wild-type group (38% and 46%, respectively, $P = 0.15$).

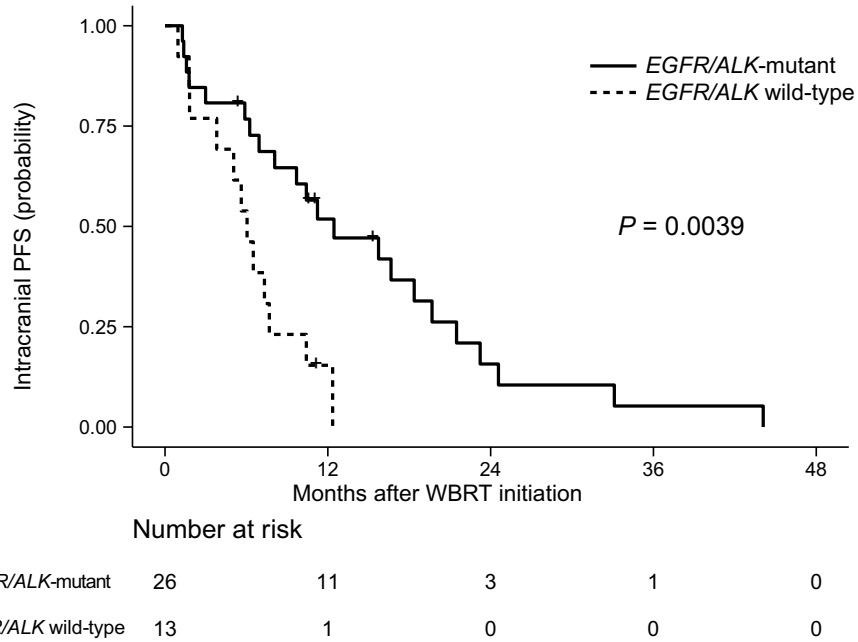

Fig. 2 Intracranial progression-free survival of patients evaluated by brain contrast-enhanced MRI before and after WBRT according to *EGFR/ALK* alteration status (n = 39). *MRI* magnetic resonance imaging, *PFS* progression-free survival, *WBRT* whole-brain radiotherapy

Table 3 Univariate analysis of intracranial PFS (n = 39[a])

Characteristic	HR	95% CI	*P*-value[b]
Age (≥ 70 vs. < 70)	1.72	0.73–4.04	0.21
Sex (male vs. female)	1.04	0.50–2.17	0.91
ECOG PS (0–1 vs. 2–3)	0.75	0.46–1.20	0.23
Brain metastasis (present vs. absent)	0.76	0.36–1.59	0.47
Hydrocephalus (present vs. absent)	0.70	0.21–2.33	0.55
Extracranial metastasis (present vs. absent)	0.84	0.38–1.83	0.66
Primary control (controlled vs. not controlled)	0.69	0.34–1.37	0.28
No. of prior systemic chemotherapy regimens (< 2 vs. ≥ 2)	1.48	0.71–3.07	0.28
EGFR/ALK (mutant vs. wild-type)	0.31	0.14–0.72	0.0039

HR hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status

[a]Patients who underwent contrast-enhanced brain MRI before and after WBRT for LM were evaluated for intracranial PFS. Intracranial disease progression was assessed using the Leptomeningeal Assessment in Neuro-Oncology scale

[b]*P*-values were calculated using the log-rank test

Relationship between OS and concurrent TKI administration in patients receiving WBRT for *EGFR*/*ALK*-mutant LM

Finally, based on the finding that the presence of *EGFR/ALK* alterations was associated with a better prognosis in patients receiving WBRT for LM, we focused on the relationship between administration of molecular targeted TKI therapy concurrent with WBRT and OS in the *EGFR*/*ALK*-mutant group. Of the 51 patients with *EGFR*/*ALK*-mutant LM, 30 received TKI therapy concurrent with WBRT. OS tended to be better in the patients receiving WBRT with concurrent TKIs versus without TKIs, although the difference was not statistically significant (median OS 15.9 [95% CI 10.4–32.7] vs. 5.9 [95% CI 3.4–20.9] months, respectively; $P = 0.23$; Supplementary Fig. 2).

Discussion

This study evaluated the prognosis of patients who received WBRT for LM originating from lung adenocarcinoma. The median OS of the patients was 6.2 months. We revealed that the presence of *EGFR/ALK* alterations was associated with better OS, even though most patients with *EGFR*/*ALK* alterations had failed at least one *EGFR*/*ALK*-TKI therapy before WBRT. This is the first study to evaluate the influence of *EGFR*/*ALK* alterations on the prognosis of patients receiving WBRT for LM from lung adenocarcinoma.

Previous studies reported a median OS from LM diagnosis of 1–11 months in patients with NSCLC [3]. Although few studies have evaluated OS from the initiation of WBRT for LM, Ozdemir et al. investigated the prognosis of 51 NSCLC patients receiving WBRT for LM and showed that the median OS from WBRT initiation was 3.9 months; however, the *EGFR*/*ALK* status was not available for most patients [9]. The median OS from WBRT initiation was 6.2 months in our study, which is consistent with previous studies.

A few studies evaluated the prognosis of *EGFR*-mutant NSCLC patients who underwent WBRT for LM and reported a median OS from LM diagnosis of 10.9–13.6 months [5, 10], which was similar to our median OS from WBRT initiation of 10.4 months in the *EGFR*/*ALK*-mutant group. However, information on LM treatment before WBRT and the *ALK* status was not described in previous studies on WBRT for LM.

The impact of *EGFR*/*ALK* alterations on patients who received WBRT for LM has not been elucidated [11]. Similar to our findings, Yin et al. developed a molecular graded prognostic assessment model using clinical variables at the time of LM diagnosis to retrospectively estimate the survival of lung cancer patients with LM [12]. They reported that the presence of *EGFR*/*ALK* alterations was a favorable prognostic factor for LM. However, only approximately 20% of patients received radiotherapy such as WBRT (the radiotherapy details were not described) in their study. Because we analyzed a single-center retrospective cohort, further studies are needed to determine more accurate prognoses of patients receiving WBRT for LM from lung adenocarcinoma.

Possible reasons for the better prognosis of the *EGFR*/*ALK*-mutant group than the wild-type group in this study are as follows. First, patients with *EGFR/ALK* alterations have more treatment options, including TKIs, after WBRT than do patients with wild-type *EGFR/ALK*. This may have prolonged the prognosis in the *EGFR/ALK*-mutant group. In this study, over 80% of the *EGFR*/*ALK*-mutant group received subsequent systemic therapy after WBRT, which was twice as high as the proportion in the wild-type group. Second, although we did not assess the efficacy of WBRT, we cannot rule out the possibility that greater radiosensitivity of *EGFR*-mutant or *ALK*-rearranged cancer cells affected LM progression. *EGFR* mutations inhibit radiation-induced EGFR translocation to the nucleus and binding to the catalytic subunit of DNA-dependent protein kinases, thereby inhibiting the repair of radiation-induced DNA double-strand breaks and increasing the radiosensitivity of *EGFR*-mutant NSCLC cells [13, 14]. Consistent with those preclinical studies, we previously reported a lower infield failure rate after proton beam therapy for *EGFR*-mutant T1-3N0M0 non-squamous NSCLC than wild-type NSCLC [15]. Brain metastases derived from *EGFR*-mutant lung adenocarcinoma show a better response to WBRT than do those derived from *EGFR*-wild-type lung adenocarcinoma [16]. Although the association between *ALK* rearrangement and the response to radiotherapy has not been established, palliative radiotherapy induces a better rate of pain relief for bone metastases originating from *ALK*-rearranged NSCLC than from *ALK* wild-type NSCLC [17]. Our findings were compatible with those studies.

This study has several limitations. First, this was a retrospective and single-center study and therefore was subject to selection bias. Second, most patients who were evaluated by brain contrast-enhanced MRI after WBRT had an ECOG PS of 0–1, and the role of the ECOG PS in intracranial PFS could not be assessed. However, the proportion of patients with *EGFR/ALK* alterations among the patients evaluated for intracranial PFS was similar to that among all 80 patients. Last, we did not perform CSF cytology in most patients mainly because the results would not have influenced the therapeutic strategies in our cohort. Moreover, CSF sampling via lumbar puncture is an invasive procedure, and the sensitivity of a single lumbar puncture is as low as 50% [3]. As stated in several guidelines, LM can be diagnosed by MRI alone, even if CSF cytology is negative or not performed [4, 7].

Conclusions

This study demonstrated patient prognosis after WBRT for LM from lung adenocarcinoma according to the *EGFR/ALK* alteration status. Although the prognosis of patients receiving WBRT for LM was poor, the presence of *EGFR/ALK* alterations and an ECOG PS of 0–1 were associated with longer OS in patients eligible for WBRT. Further studies are needed to clarify the indications and efficacy of WBRT in LM patients with *EGFR/ALK* alterations and good ECOG PS.

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Data availability All data generated or analyzed for this study are included in this published article.

Declarations

Conflict of interest All authors declare no competing interests.

Ethical approval This retrospective study was approved by the National Cancer Center Hospital East Institutional Review Board (Protocol Number 2017-440).

Consent for publication Not applicable.

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