Cancer Management and Research

Elevate Series

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ORIGINAL RESEARCH

The Effect of Intracranial Control After Intracranial Local Therapy on the Prognosis of Patients with Brain Metastasis of Lung Adenocarcinoma

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Purpose: The aim of the present study was to assess the clinical outcomes and prognostic factors of lung adenocarcinoma patients with brain metastases (BMs) after intracranial local therapy.

Patients and Methods: A total of 83 lung adenocarcinoma patients with BMs who underwent craniotomy combined with radiotherapy or intracranial radiotherapy alone were retrospectively analyzed. The intracranial tumor response was determined according to the Response Assessment in Neuro-Oncology of Brain Metastases (RANO-BM) criteria. The median overall survival (OS), intracranial progression-free survival (iPFS), and related prognostic factors were analyzed with the Kaplan–Meier estimator method and Cox proportional hazards regression model.

Results: Among 83 patients, 20 patients received craniotomy combined with radiotherapy, and 63 patients received intracranial radiotherapy alone. Following intracranial local therapy, 11 patients (13.3%) achieved complete response (CR); among them, 8 patients underwent neurosurgical resection. In addition, 32 patients (38.55%) achieved partial response (PR), 32 patients (38.55%) experienced stable disease (SD), and 8 (9.6%) experienced progressive disease (PD). The median follow-up period was 25.4 months (range 0.8–49.6 months). The median follow-up time for the iPFS was 16.2 months (range 0.6–41.2 months). The median OS, iPFS were 28.2 months and 24.7 months. Epidermal growth factor receptor (EGFR) / anaplastic lymphoma kinase (ALK) mutations (HR 3.216, 95% confidence interval (CI) 1.269–8.150, $p = 0.014$) and iPFS (HR 0.881, 95% CI 0.836–0.929, $p < 0.001$) were found to be beneficial factors for OS. An intracranial-tumor CR was associated with a longer iPFS (PR: HR 0.052, 95% CI 0.009–0.297, $p = 0.001$; SD: HR 0.081, 95% CI 0.025–0.259, $p < 0.001$; PD: HR 0.216, 95% CI 0.077–0.606, $p = 0.004$).

Conclusion: Prolonged iPFS was associated with better OS in lung adenocarcinoma patients with BMs following intracranial local therapy, and mutations of EGFR / ALK or an intracranial-tumor CR are independent prognostic factors for prolonged survival.

Keywords: lung adenocarcinoma, brain metastases, intracranial local therapy, survival, prognostic factors

Introduction

Lung cancer is a frequently occurring type of cancer in developing and developed countries, with 2,206,771 new cases and 1,796,144 deaths recorded in 2020.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, and 20% of patients experience brain metastases (BMs) at the time of diagnosis, while approximately 25% to 50% of patients develop BMs during the disease course.[2] Adenocarcinoma is the main subtype of NSCLC and is characterized by rapid progression, early distant metastasis and a significantly greater incidence of BMs than other subtypes.[3,4] For lung adenocarcinoma patients, BMs is an important cause of morbidity and mortality during the course of the disease.[5] A previous study showed that patients with BMs have relatively low quality of life and shorter lifespan of only 3–6 months when untreated.[6] However, previous studies suggested that lung adenocarcinoma is associated with

Received: 21 May 2024
Accepted: 20 July 2024
Published: 31 July 2024

a better prognosis in patients with NSCLC with BMs.[7,8] One possible explanation for this variability is that tyrosine kinase inhibitors (TKIs) against mutated driver oncogenes, such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), dramatically improve the outcome of patients with NSCLC.[9,10] In recent decades, TKIs have been demonstrated to represent an effective treatment method for the management of BMs in NSCLC patients with EGFR or ALK mutations.[11–13] The central nervous system (CNS) disease control rate of TKIs for NSCLC patients with EGFR-mutant and BMs was reported up to 93%, the median progression-free survival (PFS) and overall survival (OS) were 6.6 months and 15.9 months.[14] However, some research has indicated that the intracranial progression-free survival (iPFS) of EGFR-mutant NSCLC with BMs patients utilizing TKIs is constrained, with a range of 8 to 10 months.[15,16] The results showed that although TKIs alone were effective, their therapeutic effect was limited, emphasizing the importance of intracranial local therapy of BMs in NSCLC patients with EGFR/ALK mutations.

Intracranial local therapy, which includes surgical resection and brain radiotherapy, is a standard therapy for lung adenocarcinoma patients with BMs. The most commonly administered modes of brain radiotherapy include WBRT, local radiotherapy, and WBRT plus a radiotherapy boost (WBRT+RTB).[17,18] A plethora of research has demonstrated that intracranial local therapy enhances iPFS and OS and increases the rate of BM remission in EGFR/ALK - positive NSCLC patients with BMs.[19,20] Additionally, El Shafie et al[21] showed that early local therapy for BMs in oncogene-driven NSCLC patients prolonged the iPFS but not the OS in TKI-treated EGFR+/ALK+ NSCLC patients. Similar results were also observed in a retrospective analysis of 176 EGFR+ patients, in which upfront WBRT/TKIs did not improve OS but only iPFS, although only in patients with >3 BMs.[22] In contrast, a meta-analysis of 30 studies suggested that NSCLC patients with BMs harboring EGFR or ALK mutations have superior OS compared to wild-type (WT) patients, and no iPFS or OS benefit was found with the addition of TKIs to RT.[23] Two other randomized trials revealed that intracranial local therapy failed to improve the duration of functional independence or OS.[24,25]

Therefore, whether intracranial local therapy is beneficial for survival in NSCLC patients with BMs remains controversial. Moreover, previous studies involved mixed pathological types especially NSCLC, and there are fewer reports on the effect of intracranial local therapy on the survival of BMs from lung adenocarcinoma. Accordingly, this retrospective study was designed to summarize the prognostic factors affecting the survival and further analyze the effect of the iPFS on OS in lung adenocarcinoma patients with BMs who were treated with intracranial local therapy.

Material and Methods

Patient Selection Criteria

Lung adenocarcinoma patients with BMs who underwent intracranial local therapy at our hospital between January 2019 and March 2023 were analyzed retrospectively. The eligibility criteria were as follows: (1) age ≥ 18 years; (2) Karnofsky performance score (KPS) ≥ 60 or KPS ≥ 50 but caused only by BMs; (3) histologically proven lung adenocarcinoma; (4) BMs confirmed by contrast-enhanced magnetic resonance imaging (MRI) such as gadolinium-enhanced MRI, and a measurable disease of BMs is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion. (5) underwent intracranial local therapy (including craniotomy combined with radiotherapy or intracranial radiotherapy alone). The exclusion criteria were as follows: (1) leptomeningeal metastases; (2) synchronous or metachronous malignancies that might affect survival; (3) unfinished RT course; and (4) missing data or lost to follow-up.

This retrospective study was approved by The First Affiliated Hospital of Fujian Medical University (No. [2015]084–2) Institutional Review Board and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to treatment, and all information was anonymized prior to analysis.

Data Collection

Data related to demographic and disease characteristics, intracranial local therapy and antitumor drug therapy were collected. The demographic and disease characteristics of the enrolled patients, including sex, age, Karnofsky Performance Scale (KPS), smoking history, lung-molecular grade prognostic assessment (Lung-molGPA), which was based on age, KPS, presence of extracranial metastases, number of BMs and EGFR/ALK alterations,[26] gene mutation type, BMs number, BMs volume, and presence of extracranial metastases, were collected. The use of intracranial local therapy, including craniotomy, radiotherapy modalities and equivalent doses in 2Gy fractions (EQD2), was also analyzed. In addition, antitumor drug therapy data with or without chemotherapy, vascular targeting therapy and TKI therapy were also recorded.

Treatment

Concurrent chemotherapy was defined as chemotherapy which started less than 2 weeks before or 1 week after the initiation of RT.[27] The regimens of concurrent chemotherapy in the current study included a single regimen of pemetrexed and combined regimens of platinum plus pemetrexed or platinum plus docetaxel. The anti-vascular targeting drugs included bevacizumab, recombinant human endostatin and anlotinib. EGFR-TKIs included gefitinib, erlotinib, ectinib, afatinib, dacomitinib, almonertinib, and osimertinib. The ALK-TKIs used included crizotinib, ceritinib, alectinib, and lorlatinib.

Follow-Ups and endpoints

Patients were evaluated every 3 months for the first 2 years after CRT, every 6 months for the next 3 years, and then once annually. MRI brain is the primary modality for diagnosis and surveillance of BMs at our institution. The follow-up evaluations consisted of clinical evaluations, enhanced brain MRI, and imaging examinations of the primary tumor and extracranial metastases every 3 months. The last follow-up of the surviving patients was May 2023.

The observed indicators were OS, iPFS and the iORR. OS was defined as the time from the date of BM diagnosis to the date of death from any cause or censoring at the time of the last follow-up. iPFS was defined as the time from the initiation of intracranial local therapy (including craniotomy combined with radiotherapy or intracranial radiotherapy alone) to the date of intracranial progression (including the growth of a previous lesion and/or the development of a new lesion), death due to any cause, or the last day of follow-up. The iORR was defined as the percentage of patients who achieved an intracranial complete or partial response, which was evaluated based on the Response Assessment in Neuro-Oncology of Brain Metastases (RANO-BM) criteria.[28]

Statistical Analyses

The data were analyzed using SPSS version 26.0 (IBM Corp, Armonk, NY, USA) and the statistical programming language R version 4.0.4. Survival curves were generated using the Kaplan–Meier estimator method and compared with the Log rank test. Univariate and multivariate analyses used the COX proportional hazards regression model to assess prognostic factors for OS and iPFS. After univariate analysis, clinical factors with $P < 0.05$ were included in the multivariate Cox proportional hazards regression model for analysis. The confidence intervals (CIs) represented the 95% lower and upper bounds. $P < 0.05$ was considered indicative of statistical significance.

Results

Patient Characteristics

Eighty-three patients were eligible for this study (Figure 1). The patient baseline characteristics are listed in Table 1. Fifty-four (65.1%) patients were male, and 29 (34.9%) were female. The median age in the entire cohort was 57 years (range, 29–78). The Karnofsky Performance Scale (KPS) score ranged from 50–90, and 9 patients (10.8%) had a Karnofsky Performance Scale (KPS) score < 80. Forty-seven (56.6%) patients had EGFR/ALK mutations, 12 (14.5%) had other types of mutations, and 24 (28.9%) had WT or unknown mutations. The median BMs number and volume were 3 (range, 1–8) and 18.82 cc (range, 0.46–163.38), respectively. 20 patients (24.1%) with BMs underwent

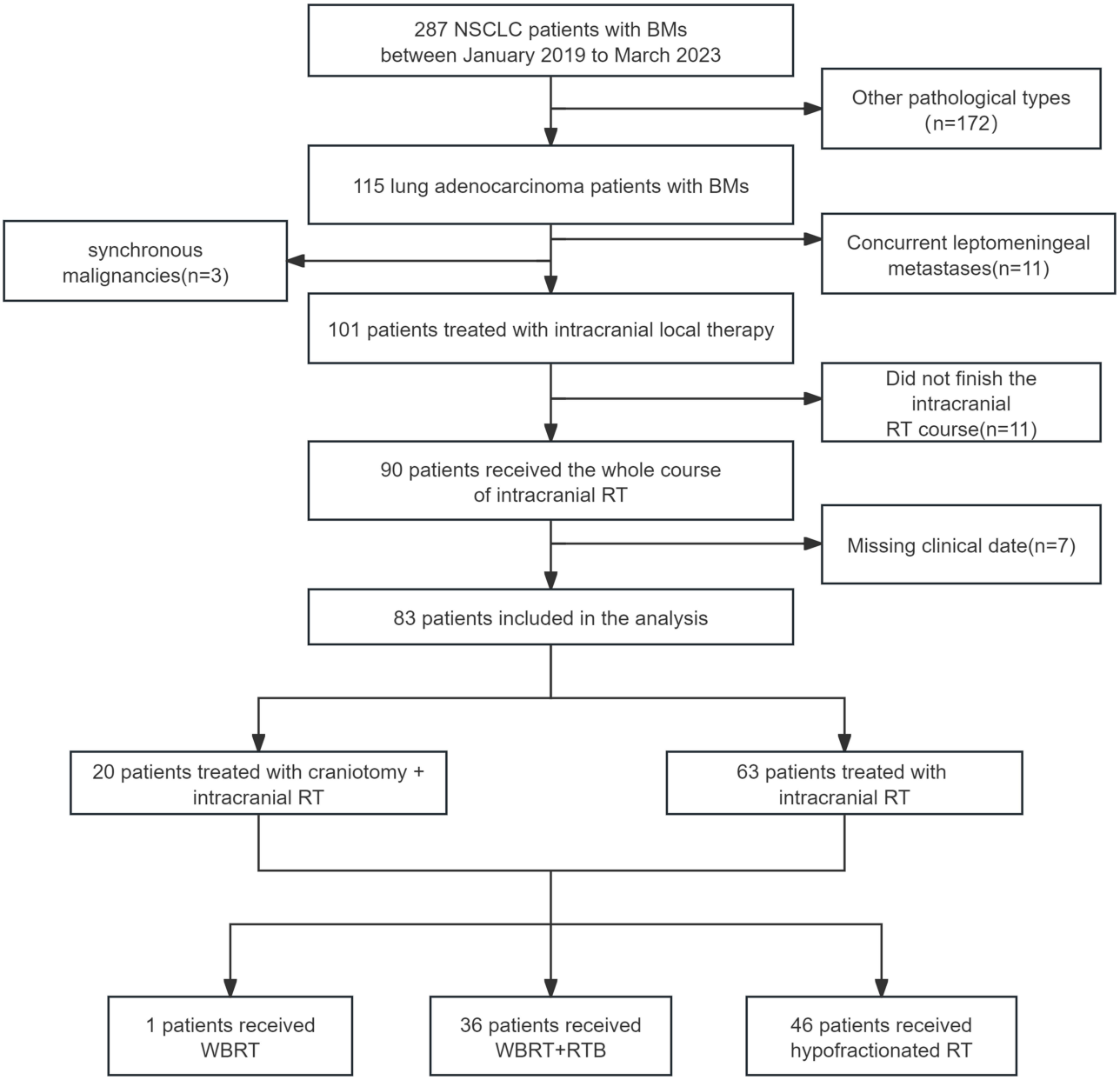

Figure 1 Flowchart of the study.

surgical resection. Thirty-seven patients (44.6%) underwent WBRT, of which 36 patients (97%) underwent concurrent RT of local lesions (WBRT plus a radiotherapy boost, WBRT+ RTB) with a median dose of 46 Gy/20F (range, 31.5–60 Gy/9–25F, 5F/week). Forty-six patients (55.4%) underwent hypofractionated radiotherapy with a median dose of 45.6 Gy/12 F (range, 30–48 Gy/5-16 F, 5 F/week), while 5 patients underwent low-fraction conventional radiotherapy of local lesions with a median dose of 48 Gy (range, 48–60 Gy). A total of 48 patients (57.8%) received TKIs as the first-line treatment. In addition, 25 patients (30.1%) received concurrent chemotherapy (Table 2).

iORR

The iORR in the entire cohort was 51.85%. Following intracranial local therapy, 11 patients (13.3%) achieved complete response (CR); among them, 8 patients underwent neurosurgical resection. In addition, 32 patients (38.55%) achieved partial response (PR), 32 patients (38.55%) experienced stable disease (SD), and 8 (9.6%) experienced progressive disease (PD).

Table 1 Clinical Characteristics of Patients

Characteristics	Total N (%)
Sex	
Male	54(65.1)
Female	29(34.9)
Age (years)	
≥60	35(42.2)
<60	48(57.8)
KPS	
≥80	74(89.2)
<80	9(10.8)
Lung-molGPA	
1–1.5	15(18.1)
2–4	68(81.9)
Smoking	
Yes	31(37.3)
No	52(62.7)
Gene-mutation type	
EGFR/ALK mutations	47(56.6)
Other mutations	12(14.5)
Negative/Unclear	24(28.9)
EQD2 (Gy)	
≥52	34(41.0)
<52	49(59.0)
BMs number	
1–3	44(53.0)
≥4	39(47.0)
BMs volume	
≥9.6cc	57(68.7)
<9.6cc	26(31.3)
Extracranial metastases	
Yes	46(55.4)
No	37(44.6)

Abbreviations: ALK, anaplastic lymphoma kinase; BMs, brain metastases; EGFR, epidermal growth factor receptor; EQD2, equivalent dose in 2 Gy/f; KPS, Karnofsky Performance Score; Lung-molGPA, lung-molecular grade prognostic assessment; N, number.

Intracranial Progression-Free Survival

The median follow-up time for the iPFS was 16.2 months (range 0.6–41.2 months). The median iPFS was 24.7 months (range 0.6–41.2 months). Factors that positively influenced iPFS in the univariate analysis included EGFR/ALK mutations (P=0.008, Figure 2A), BMs volume ≥ 9.6 cc (P=0.022, Figure 2B), and intracranial-tumor CR (PR: P<0.001; SD: P<0.001; PD: P=0.003, Figure 2C). Multivariate analysis revealed that intracranial-tumor CR (PR: HR, 0.052; 95% CI, 0.009–0.297; P=0.001; SD: HR, 0.081; 95% CI, 0.025–0.259; P<0.001; PD: HR, 0.216; 95% CI, 0.077–0.606; P =0.004) was associated with iPFS (Table 3). Notably, patients with BMs volume < 9.6 cc exhibited worse iPFS than patients with BMs volume ≥ 9.6 cc. However, this difference was not statistically significant in the multivariate analysis (Table 3).

Table 2 Treatment of Patients

Treatment	Total N (%)
Craniotomy	
Yes	20(24.1)
No	63(75.9)
Vascular targeting therapy	
Yes	24(28.9)
No	59(71.1)
Concurrent chemotherapy[a]	
Yes	25(30.1)
No	58(69.9)
TKI therapy	
Yes	48(57.8)
No	35(42.2)
Radiotherapy modalities	
WBRT±RTB	37(44.6)
Hypofractionated RT	46(55.4)

Notes: [a]Concurrent chemotherapy was defined as chemotherapy which started less than 2 weeks before or 1 week after the initiation of RT.
Abbreviations: N, number; TKI, tyrosine kinase inhibitor; WBRT±RTB, whole brain radiation therapy±radiotherapy boost.

Overall Survival

The median follow-up time was 25.4 months (range 0.8–49.6 months). At the last follow-up, 48 patients remained alive, and 35 patients died. Among these patients, 23 (65.7%) died of BM progression, 11 (31.4%) died of extracranial metastases, and 1 (2.9%) died of internal medical disease. The median OS was 28.2 months (range 0.8–49.6 months).

Univariate and multivariate analyses were performed to determine the prognostic indicators for OS (Table 3, Supplementary Table). Univariate analysis revealed that a Lung-molGPA score of 1–1.5 (P=0.012, Figure 3A), smoking status (P=0.049, Figure 3B), EGFR/ALK mutation status (P=0.001, Figure 3C), TKI therapy (P=0.042, Figure 3D), intracranial-tumor CR (PR: P=0.006; SD: P<0.001; PD: P=0.004, Figure 3E) and iPFS (P<0.001) were significant factors influencing OS (Table 3). However, multivariate analysis revealed that only EGFR/ALK mutations (HR, 3.216; 95% CI, 1.269–8.150; P = 0.014) and iPFS (HR, 0.881; 95% CI, 0.836–0.929; P <0.001) were independent factors associated with OS (Table 3). No difference in OS was observed between the four groups for patients with a Lung-molGPA score of 1–1.5 or 2–4 (P=0.322), smoking status of yes or no (P=0.724), TKI therapy of yes or no (P=0.949) or intracranial-tumor CR (PR: P=0.550; SD: P=0.307; PD: P=0.112). The median OS of patients with EGFR/ALK mutations and the median iPFS were 33.8 and 25.5 months, respectively.

Discussion

In this study, we found that prolonged iPFS was associated with better OS in lung adenocarcinoma patients with BMs following intracranial local therapy. Moreover, lung adenocarcinoma patients with BMs harboring EGFR/ALK mutations exhibited longer OS than did patients with BMs harboring EGFR/ALK-negative/unclear mutations but did not experience significantly prolonged median iPFS. Furthermore, patients who achieved intracranial-tumor CR experienced the best iPFS.

Deng et al draw a similar conclusion that prolonged iPFS translates into a better OS in EGFR-mutant lung adenocarcinoma patients with BM who received TKIs combined with craniocerebral radiotherapy.[29] In contrast to our findings, another study by Deng et al showed that in low scores of Lung-molGPA patients with EGFR-mutant lung adenocarcinoma with BMs, the enhanced iPFS failed to translate to improved OS among three brain radiotherapy modes.[30] Given the correlation between iPFS and OS after intracranial local therapy for BMs of lung adenocarcinoma

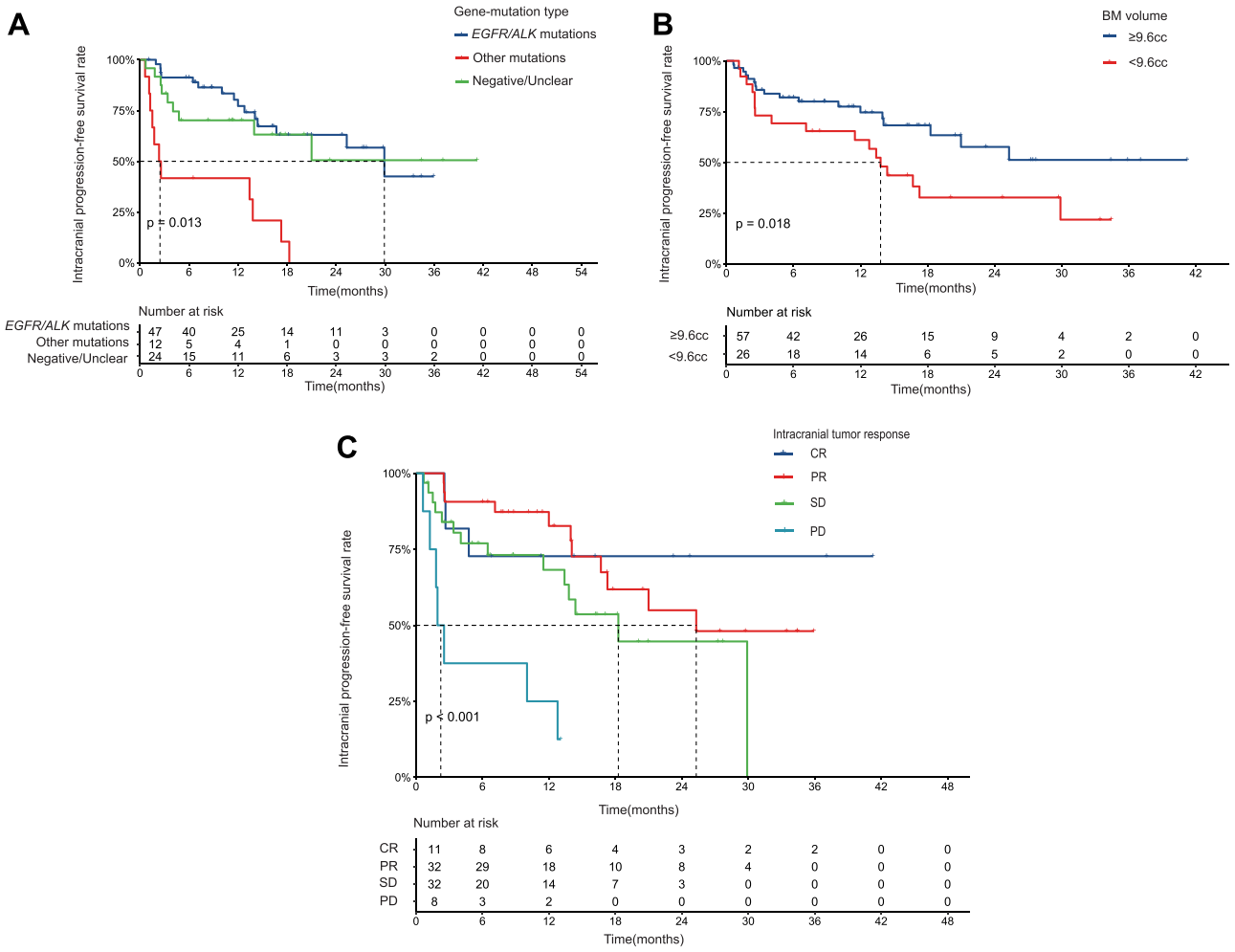

Figure 2 The iPFS in various subgroups of independent significant factors Gene-mutation type (**A**), BMs volume (**B**) and Intracranial tumor response (**C**).

patients is controversial, and there are fewer relevant reports, the findings of the current study can contribute to the data in the literature database.

Although our results suggest that intracranial local therapy can translate the prolongation of iPFS into an improvement in OS, the high CNS control rate of TKIs and the neurologic function deficit from intracranial local therapy have been suspected in the era of TKIs. Based on the results of our analysis, lung adenocarcinoma patients with BMs harboring EGFR/ALK mutations (33.8 months; $p = 0.014$) appear to have superior median OS as compared to negative/unclear patients (22.8 months) with no significant difference noted with regards to iPFS after intracranial local therapy. Consistent with our findings, NSCLC patients with BMs harboring EGFR (20.9 months; $p = 0.0006$) or ALK mutations (48.5 months; $p < 0.0001$) have superior OS but not prolonged iPFS compared to WT patients.[23] Similarly, Arrieta O et al reported that the presence of EGFR mutations (36.6 months) is associated with longer OS in NSCLC patients with BMs.[31] Another report also revealed that EGFR mutation (14.5 months) was associated with longer OS in NSCLC patients with BMs, but there was no significant difference in clinical response.[32] In contrast, a retrospective study indicated that early local therapy improved iPFS but not OS in patients with BMs of EGFR+/ALK+ NSCLC.[22] In a small cohort of NSCLC patients with BMs, Lee et al demonstrated that EGFR mutation status in NSCLC patients with BMs is associated with a greater ORR and longer iPFS compared with wild-type EGFR.[33] Notably, our study showed that EGFR/ALK mutations and treatment with TKIs are prognostic factors associated with long-term survival in lung adenocarcinoma patients with BMs. However, multivariate analysis revealed that TKI therapy did not improve OS in lung adenocarcinoma patients with BMs following intracranial local therapy. This result may be due to the intracranial

Table 3 Positive Prognostic Factors by Univariate and Multivariate Analyses

Variables	iPFS						OS					
	Univariable Analysis			Multivariable Analysis			Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Lung-molGPA												
1–1.5 vs 2–4	1.001	0.348–2.875	0.999				0.386	0.184–0.811	0.012	0.600	0.218–1.650	0.322
Smoking												
Yes vs No	0.467	0.211–1.032	0.060				0.504	0.255–0.997	0.049	0.852	0.350–2.076	0.724
Gene-mutation type												
EGFR/*ALK* mutations		Reference			Reference			Reference			Reference	
Other mutations	1.611	0.629–4.123	0.320	1.074	0.373–3.092	0.895	0.716	0.310–1.655	0.434	0.993	0.421–2.343	0.988
Negative/Unclear	4.888	1.505–15.878	0.008	3.144	0.862–11.462	0.083	4.411	1.786–10.894	0.001	3.216	1.269–8.150	0.014
TKI therapy												
Yes vs No	0.712	0.323–1.567	0.399				1.999	1.026–3.896	0.042	0.964	0.317–2.930	0.949
BMs volume												
≥9.6cc vs <9.6cc	2.285	1.127–4.629	0.022	1.886	0.920–3.864	0.083	1.599	0.820–3.117	0.168			
Intracranial tumor response												
CR		Reference			Reference			Reference			Reference	
PR	0.042	0.008–0.239	<0.001	0.052	0.009–0.297	0.001	0.141	0.035–0.565	0.006	0.602	0.114–3.184	0.550
SD	0.077	0.024–0.245	<0.001	0.081	0.025–0.259	<0.001	0.169	0.063–0.458	<0.001	0.504	0.136–1.876	0.307
PD	0.214	0.076–0.601	0.003	0.216	0.077–0.606	0.004	0.252	0.098–0.649	0.004	0.396	0.126–1.241	0.112
iPFS							0.868	0.822–0.916	<0.001	0.881	0.836–0.929	<0.001

Abbreviations: ALK, anaplastic lymphoma kinase; BMs, brain metastases; CI, confidence interval; CR, complete responses; EGFR, epidermal growth factor receptor; EQD2, equivalent dose in 2 Gy/f; HR, hazard ratios; KPS, Karnofsky Performance Score; Lung-molGPA, lung-molecular grade prognostic assessment; N, number; PR, partial responses; PD, progressed disease; SD, stable disease; TKI, tyrosine kinase inhibitor; WBRT±RTB, whole brain radiation therapy ±radiotherapy boost.

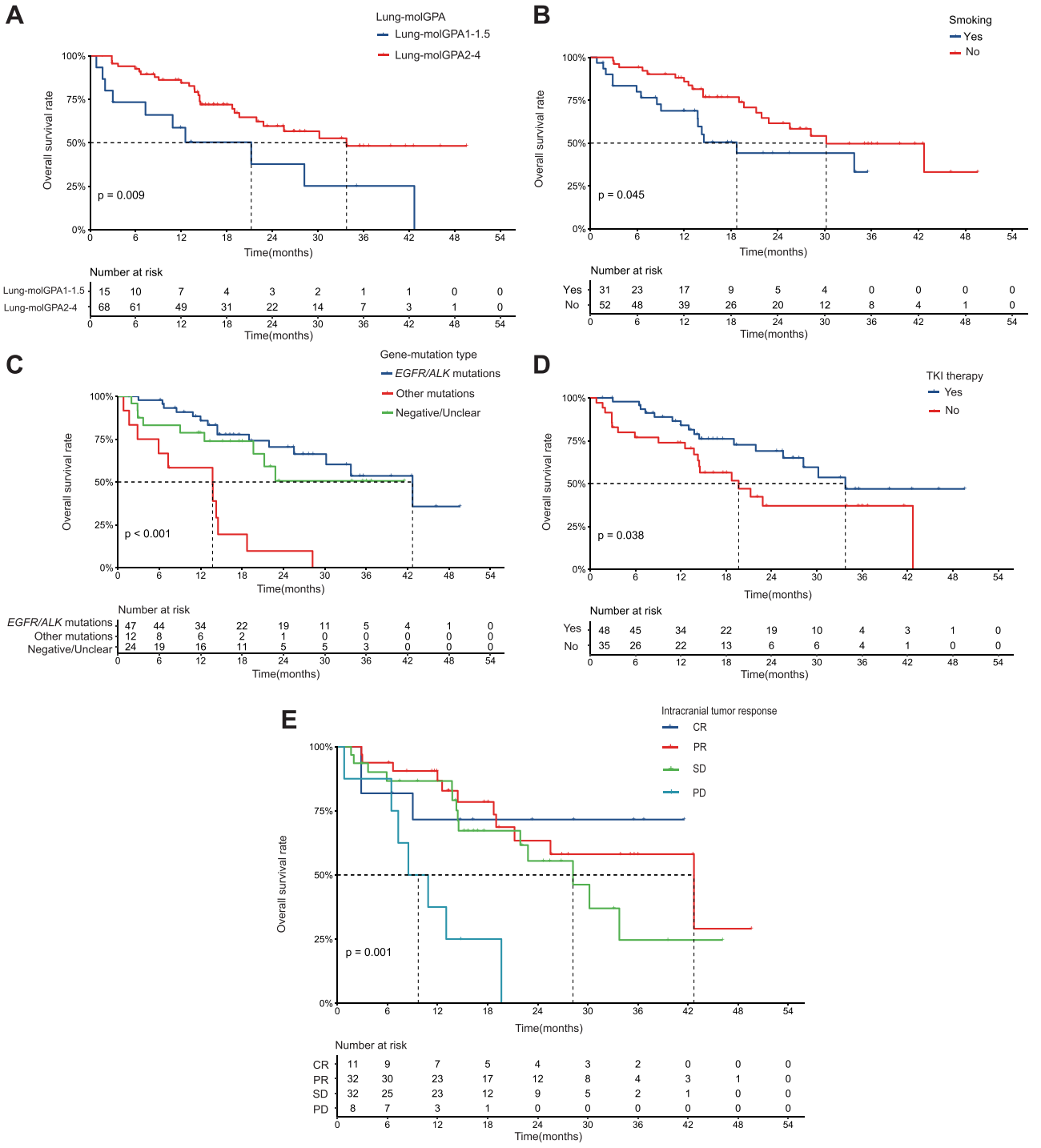

Figure 3 The OS in various subgroups of independent significant factors Lung-molGPA (**A**), Smoking (**B**), Gene-mutation type (**C**), TKI therapy (**D**) and Intracranial tumor response (**E**).

activity of TKIs; less than half of our patients in our study received newer generations of TKIs relative to first-generation TKIs, and our study may have underestimated the favorable survival of BM patients with EGFR/ALK alterations who received newer, highly CNS-active TKIs.[34,35]

We also found that patients with an iORR of CR had a longer miPFS, which was consistent with the results reported previously.[36] Although it translated into an increase in iPFS, the increased intracranial tumor control did not translate into a prolonged OS. This may be due partly to the small number of samples in this study. In our study, the iORR in the entire

cohort was 51.85%, and the iORR of patients with EGFR/ALK mutations was 53.2%, which was greater than that of patients with other types of mutations and WT patients. Multiple retrospective studies have examined whether the EGFR/ALK mutation status results in improved survival and response to treatment after intracranial RT for BMs from lung adenocarcinoma. Lee et al[33] demonstrated that mutant EGFR in NSCLC patients is an independent prognostic factor for longer intracranial radiological progression-free survival following intracranial RT for BMs, and the response rate was significantly higher in patients with EGFR mutations than those with the WT (80% vs 46%; p = 0.037). Gow et al[37] observed that lung adenocarcinoma patients with BMs with mutant EGFR (46%) had a roughly two times higher ORR than that of the WT group following WBRT. Nevertheless, another study showed no significant difference in brain RT response among NSCLC patients with and without EGFR mutations.[32] Notably, the majority of patients who underwent surgical resection of a single BM followed by intracranial radiotherapy achieved CR. This phenomenon may be related to the nature of BMs. Surgery is especially indicated when the brain lesion is large, the patient is symptomatic due to elevated intracranial hypertension, and the tumor is preferably located in a nonfunctional region.[38] Numerous studies have shown that neurosurgical resection of a single BM followed by WBRT significantly improves survival compared with WBRT alone.[39,40] Taken together, these findings indicated that the iORR is a useful predictor of survival in NSCLC patients with BMs following intracranial local therapy. In particular, achieving CR is associated with improved iPFS, while patients who do not respond to treatment have worse outcomes. These results highlighted the importance of monitoring the response to treatment and considering alternative therapies for patients who did not achieve a response.

There are some limitations to the present study. First, this was a retrospective study with inherent biases. Second, the sample size of this study was small. Third, due to the incomprehensiveness of retrospective medical records, we could not provide an accurate incidence of long-term neurological adverse effects such as cognitive brain function. In the future, more rigorous and prospective clinical studies with large sample sizes should be designed to provide a comprehensive understanding of the intracranial efficacy of intracranial local therapy in patients with BMs from lung adenocarcinoma and further analyze the effect of the iPFS on OS, thereby helping to manage survivorship of intracranial disease.

Conclusion

In lung adenocarcinoma patients with BMs who receive intracranial local therapy, prolonged iPFS translates into a better OS, and mutations of EGFR / ALK or an intracranial-tumor CR are independent prognostic factors for prolonged survival.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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