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Combination of Whole-Brain Radiotherapy with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Improves Overall Survival in EGFR-Mutated Non-Small Cell Lung Cancer Patients with Brain Metastases

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Abstract: Brain metastases (BM) cause morbidity and mortality in patients with non-small cell lung cancer (NSCLC). The use of upfront epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and withholding of whole-brain radiation therapy (WBRT) is controversial. We aim to investigate the impact of WBRT on overall survival (OS). After screening 1384 patients, a total of 141 EGFR-mutated patients with NSCLC and BM were enrolled. All patients received EGFR-TKIs between 2011 and 2015. Ninety-four patients (66.7%) were treated with WBRT (TKI + WBRT group). With a median follow-up of 20.3 months (95% confidence interval (CI), 16.9–23.7), the median OS after the diagnosis of BM was 14.3 months (95% CI, 9.5 to 18.3) in the TKI + WBRT group and 2.3 months (95% CI, 2 to 2.6) in the TKI alone group. On multivariate analysis, WBRT ($p < 0.001$), female, surgery to primary lung tumor, and surgery to BM were associated with improved OS. The 1-year OS rate was longer in the TKI+WBRT group than that in the TKI alone group (81.9% vs. 59.6%, $p = 0.002$). In conclusion, this is the first study to demonstrate the negative survival impact from the omission of WBRT in patients with EGFR-mutant NSCLC.

Keywords: brain metastases; epidermal growth factor receptor; non-small cell lung cancer; whole-brain radiotherapy; tyrosine kinase inhibitors

1. Introduction

Globally, lung cancer is a leading cause of cancer incidence and mortality [1], and is also the most common primary site of brain metastases (BM) [2]. The mainstay of treatment for BM has been surgery, whole-brain radiotherapy (WBRT) or stereotactic radiosurgery performed alone or in combination. WBRT targets any micro-metastases not detected on imaging, prevents intracranial recurrence, and reduces the risk of deaths due to neurological cause [3]. Because BM causes neurological decline, WBRT improves neurological function with minimal complications [4,5]. In 1954, it was reported to lessen headache, aphasia, hemiplegia, paralysis, blurred vision and incontinence [4]. On the other hand, radiotherapy (RT)-induced dementia in patients cured of BM was 1.9 to 5.1% [6].

Post-operative WBRT is usually recommended to prevent local recurrence and death from neurologic cause [7]. With the advance of modern treatment and improved cancer survival, the cognitive effect of WBRT is now a concern [8]. Even though the European Organization for Research and Treatment of Cancer (EORTC) 22952-26001 study revealed that post-operative adjuvant WBRT reduces intracranial relapses and neurologic deaths [9], another EORTC Phase-III trial reported an induced inferior quality of life [10]. A secondary analysis of EORTC 22952-26001 found no significant survival benefit to WBRT among patients with non-small cell lung cancer (NSCLC) and favorable Graded Prognostic Assessment (GPA) scores [11].

NSCLC accounts for approximately 85% of lung cancers [12]. It is characterized by a high incidence of BM. Advances in the understanding of genetic aberrations associated with NSCLC have led to the development of epidermal growth factor receptor (EGFR)-targeted therapies [12]. Patients with EGFR-mutated lung cancer tend to have longer survival rates, but a higher incidence of brain metastases [13]. WBRT alone is now the treatment of choice for patients who are poor candidates for surgery, yet a recent randomized controlled trial suggested no benefit of WBRT to optimal supportive care with dexamethasone in patients with poor performance status and multiple BM from NSCLC [14]. The fast-paced development of novel agents is allowing improved outcomes for patients with advanced NSCLC. Whether deferring WBRT compromises neurological and survival outcome is still under debate [15].

The optimal management of EGFR-mutated NSCLC with BM continues to develop, with new approaches to diagnosis and a continual expansion of available treatment options for patients with EGFR mutation. Current studies have reported that EGFR-mutated NSCLC exhibits better efficacy of RT than does EGFR wild-type [16–18]. Cell studies have proven that clonogenic survival of EGFR-mutated NSCLCs in response to RT was reduced 500- to 1000-fold compared with wild-type [19]. WBRT affects the blood-tumor barrier [20–23], and blood-brain barrier (BBB) disruption after WBRT treatment is documented to lead to an increase in drug permeability. Furthermore, TKI can increase the radiosensitivity of EGFR-mutated cells [23]. TKIs have different capacity to cross the BBB. In one study, the cerebrospinal fluid (CSF)-to-plasma ratio of gefitinib in patients with BM was higher than that in patients without BM (1.34% vs. 0.36%, $p < 0.001$) [24], while another study found that the BBB permeation rate of erlotinib was 4.4 ± 3.2% [25]. Hoffknecht et al. reported data from one patient with an impressive response showed an afatinib concentration in the CSF of nearly 1 nMol [26]. In the BLOOM study, the BBB permeation rate of osimertinib was found to be 16% [27].

The efficacy of TKIs with and without WBRT has not been determined in patients with BM resulting from EGFR-mutated NSCLC; thus, we aimed at identifying optimal therapeutic strategies for patients with BM in the setting of dominant oncogenic-driven disease. We hypothesized that WBRT in addition to TKI alone may offer survival benefits under the radiobiological rationale of the impact of

WBRT on BBB permeability. To address this issue, we assessed the effectiveness of TKI given alone or in combination with WBRT to patients with EGFR-mutated NSCLC and newly diagnosed BM.

2. Patients and Methods

2.1. Ethics Approval Statement

The present study (KMUHIRB-E(II)-20180185) was approved by the ethical and research committee of the Kaohsiung Medical University Hospital. This study was conducted in compliance with institutional review board regulations in accordance with the Helsinki Declaration of 1975 as revised in 1983. All patients provided written informed consent for treatment; patient information was anonymized and de-identified before analysis; consequently, all data were analyzed anonymously.

2.2. Patients

Of 1384 NSCLC patients in the database of the tertiary hospital, we identified and analyzed 141 consecutive patients with pathologically proven lung adenocarcinoma who had received TKIs between 3 January 2011 and 29 December 2015. Their BM were diagnosed by either cytology or brain neuroimaging studies. The inclusion criteria for this study were pathologically proven positive EGFR mutations, the diagnosis of BM, and the use of TKI. The exclusion criteria were a history of prior brain RT, or a history of malignancies other than lung cancer, or EGFR-TKI resistance mutation, or incapability to receive EGFR-TKI. Patient follow.ups were conducted by clinic visits or telephone calls until June 2018.

The following variables were collected: age, gender, initial clinical tumor and nodal classification, time from initial diagnosis to BM, extracranial metastasis, histological grading, EGFR mutation, operation to primary lung tumor, number of lines of chemotherapy, name of EGFR-TKI, number of lines of TKI, mean duration of TKI use, Eastern Cooperative Oncology Group (ECOG) performance status at the time of BM, number of BM, smoking history, whether the patient was symptomatic from BM, size of the largest BM, number of BM and disease-specific Graded Prognostic Assessment (dsGPA). The dsGPA was calculated for each patient to determine whether the cohorts shared similar prognostic features [28].

2.3. Target Therapy

All patients underwent pretreatment workups comprising a physical examination, a history review, chest radiography, bronchoscopy with a tumor biopsy, chest computed tomography (CT), brain magnetic resonance imaging (MRI) or CT, and routine laboratory studies. The tumor stage was classified according to the seventh edition of the Cancer Staging Manual and Handbook of the American Joint Committee on Cancer (AJCC) [29]. All patients started taking EGFR-TKI once the diagnosis of stages IIIB –IV lung cancer with EGFR mutation was established. TKIs included gefitinib, erlotinib, afatinib and osimertinib. The first generation was used and then shifting to the second or third generation might be chosen at the discretion of the thoracic oncologist.

2.4. WBRT

Ninety-four patients had WBRT once the diagnosis of BM was confirmed. For WBRT, each patient was simulated in the supine position in a customized thermoplastic immobilization mask. Three-dimensional conventional radiotherapy (3D-CRT) was delivered using a 2100 C/D linear accelerator (Varian Medical Systems, Palo Alto, CA, USA) for 57 patients. The remaining 37 patients were treated by intensity-modulated radiotherapy (IMRT) either with a Hi-Art helical tomotherapy unit, version 2.2.4.1 (TomoTherapy, Inc., Madison, WI, USA), or Eclipse, version 8.6 (Varian Medical Systems Inc., Palo Alto, CA, USA). For the 37 patients who had a boost dose to their BM, the tumor and boost beams were combined in one integrated treatment plan. Fractionation schemes were as follows: 30 Gy in 10 fractions with or without a simultaneous boost to the brain of 45 Gy, or 37.5 Gy in

15 fractions with or without a simultaneous boost to the brain of 45 Gy. The decision whether to give a RT dose boost to the BM sites was at the discretion of each radiation oncologist. The mean radiation dose was 3781 ± 749 cGy to BM.

2.5. Statistical Analysis

The primary end points were overall survival (OS) and the OS after a diagnosis of BM (OSm). OS was defined as the time from the date of lung cancer diagnosis to the date of death from any cause or until the date of the last follow-up. OSm was defined as the time from the date of BM diagnosis to the date of death from any cause or until the date of the last follow-up. OS and OSm rates were assessed by Kaplan–Meier methods and the log-rank test was used to compare time-to-event distributions. The data set was stratified and outcomes were compared by *t*-test or chi-squared test. Univariate analyses and a multivariate Cox proportional hazards regression were used to inspect all collected variables. Estimated risks of death were calculated using hazard ratios (HR) with 95% confidence intervals (CIs). The level of statistical significance was set at $p < 0.05$; all reported p values were two-tailed. The analyses were performed using the SPSS software package, version 19.0 for Windows (SPSS, Chicago, IL, USA).

3. Results

3.1. Patient Characteristics

One hundred forty-one patients out of 1384 patients were retrospectively enrolled after the aforementioned inclusion and exclusion criteria were applied. Gender difference existed in terms of smoking status (never vs. ever); 98.9% of the female patients and 37.7% of the male patients had never smoked ($p < 0.001$). The median duration of TKI use was 13.2 months (95% confidence interval (CI), 10.1 to 16.2) in TKI + WBRT group and 10 months (95% CI, 7.3 to 12.8) in the TKI alone group. The mean durations of TKI use were 18.1±15.1 months and 15.4 ± 16.4 months for patients with and without WBRT, respectively ($p = 0.327$). In this cohort of 141 patients, 52 patients had more than one line of TKIs due to intolerance or disease progression. Table 1 summarizes the clinical characteristics of the 141 patients, divided by whether they had WBRT (TKI + WBRT group vs. TKI alone group).

All of them had EGFR-TKI. The mean and median age of this retrospective cohort was 64.5 years and 62 years respectively. Ninety-four patients (66.7%) received WBRT, and 47 patients (33.3%) did not. Patients who received WBRT were more likely to have surgery to their BM (38.3% in the TKI + WBRT group and 14.9% in the TKI alone group; $p = 0.004$); neurological symptoms (76.6% in the TKI + WBRT group and 53.2% in the TKI alone group; $p = 0.005$); larger BM (70.2% over 1 cm in the TKI + WBRT group and 53.2% in the TKI alone group; $p = 0.046$); and more BM ($p = 0.043$). No significant differences were observed in terms of age, gender, stage, initial clinical tumor and nodal classification, extracranial metastases, histological grading, EGFR mutation, primary lung surgery, number of lines of chemotherapy, name of EGFR-TKI, number of lines of TKI, mean duration of TKI use, smoking history, ECOG performance status at the time of BM, and dsGPA (all $p > 0.05$; Table 1).

Table 1. Patient characteristics.

	All	WBRT	No WBRT	*p*-Value
No. of cases	141	94	47	
Age				0.112
≦40	5	4	1	
41–70	100	71	29	
>70	36	19	17	
Sex				0.389
Female	88	61	27	
Male	53	33	20	

Table 1. *Cont.*

	All	WBRT	No WBRT	*p*-Value
Initial Clinical stage				0.052 (Fisher)
I–II	8	8	0	
III–IV	133	86	47	
Initial clinical T classification				0.788
1 or 2	38	26	12	
3 or 4	103	68	35	
Initial clinical N classification				0.319
0 or 1	50	36	14	
2 or 3	91	58	33	
Histological grade				0.639
1–2	59	37	22	
3	31	23	8	
NA	51	34	17	
EGFR mutation				
Exon 18	2	1	1	0.557 (Fisher)
Exon 19	63	45	18	0.281
Exon 20	15	8	7	0.247
Exon 21	60	38	22	0.47
NA	5	3	2	0.541 (Fisher)
Lung surgery				0.393
No	121	79	42	
Yes	20	15	5	
Number of lines of systemic chemotherapy				0.078
0–2	104	65	39	
>2	37	29	8	
TKI				
afatinib	17	12	5	0.715
erlotinib	75	52	23	0.474
gefitinib	97	62	35	0.304
osimertinib	5	4	1	0.665 (Fisher)
Number of lines of TKI				0.902
1	89	59	30	
>1	52	35	17	
Mean TKI duration (months ± SD)	17.2 ± 15.6	18.1 ± 15.1	15.4 ± 16.4	0.327
ECOG				0.172
0	71	50	21	
1	62	41	21	
2	8	3	5	
Smoking				0.29
Never	107	75	32	
Former	17	9	8	
Current	17	10	7	
Brain surgery				0.004
No	98	58	40	
Yes	43	36	7	
Symptomatic brain metastases				0.005
No	44	22	22	
Yes	97	72	25	
Size of largest brain tumor				0.046
≦1 cm	50	28	22	
>1 cm	91	66	25	

Table 1. *Cont.*

	All	WBRT	No WBRT	*p*-Value
No. of brain metastases				0.043
1	33	17	16	
2–3	15	13	2	
>3	93	64	29	
Extracranial metastases				
Lung	60	34	26	0.03
Bone	106	69	37	0.491
Liver	24	15	9	0.635
dsGPA				0.898
0.5–1.5	97	65	32	
2–4	44	29	15	

Abbreviations: WBRT: whole-brain radiation therapy; EGFR: Epidermal Growth Factor Receptor; TKI: tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; dsGPA: disease-specific Graded Prognostic Assessment. * By *t*-test ** By Chi-square test.

3.2. OS and OSm

The median OS was 20.3 months (95% CI, 16.9 to 23.7) for the entire cohort. Seventeen and two patients were still alive in the TKI+WBRT group (18.1%) and TKI alone group (4.3%), respectively. The mean OS was longer for patients with WBRT (27.2 ± 16.7 vs. 21.6 ± 20.4 months, $p = 0.033$)

The median OSm was 10.5 months (95% CI, 7.2 to 13.9) for the entire cohort. The combination group survived much longer after the diagnosis of BM. The median OSm was 14.3 months (95% CI, 9.5 to 18.3) in the TKI + WBRT group and 2.3 months (95% CI, 2 to 2.6) in the TKI alone group. The mean survival after BM was 18 ± 15.2 months and 7.1 ± 10.8 months for patients with and without WBRT, respectively ($p < 0.001$).

The 1-year OS rates were 81.9% and 59.6% with and without WBRT ($p = 0.002$). WBRT ($p = 0.002$), younger age ($p = 0.003$), female gender ($p = 0.029$) and surgery to primary lung cancer ($p = 0.03$) were favorable prognostic factors for longer 1-year OS rate (Table 2). WBRT was a favorable prognostic factor for longer OS ($p = 0.034$; Figure 1A). To investigate the prognostic factors, we included five factors with $p < 0.025$ (WBRT, female gender, surgery to primary lung tumor, surgery to BM and smoking status) in a multivariable model (Table 3). WBRT was a strong favorable prognostic factor for longer survival ($p < 0.001$; Figure 1B).

Table 2. 1-year overall survival rate.

	No. of Cases	1-Year Survival Rate (Number)	*p*-Value
WBRT			0.002
No	47	59.6% (28)	
Yes	94	81.9% (77)	
Age			0.003
≦40	5	100% (5)	
41–70	100	80% (80)	
>70	36	55.6% (20)	
Gender			0.029
Female	88	80.7% (71)	
Male	53	64.2% (34)	
Initial Clinical stage			0.39
I–II	8	87.5% (7)	
III–IV	138	73.7% (98)	
Clinical Tumor classification			0.386
1 or 2	38	78.9% (30)	
3 or 4	103	72.8% (75)	
Clinical Nodal classification			0.127
0 or 1	50	82% (41)	
2 or 3	91	70.3% (64)	

Table 2. *Cont.*

	No. of Cases	1-Year Survival Rate (Number)	*p*-Value
Extracranial metastases			
Lung	60	78.3% (47)	0.4
Bone	106	71.7% (76)	0.203
Liver	24	70.8% (17)	0.675
Lung surgery			0.03
No	121	71.1% (86)	
Yes	20	95% (19)	
Brain surgery			0.593
No	111	75.7% (84)	
Yes	30	70% (21)	
ECOG			0.299
0	71	76.1% (54)	
1	62	75.8% (47)	
2	8	50% (4)	
Smoking			0.243
Never	107	75.7% (81)	
Former	17	82.4% (14)	
Current	17	58.8% (10)	
Symptomatic brain metastases			0.219
No	44	68.2% (30)	
Yes	97	77.3% (75)	
Size of largest brain tumor			0.357
≦1 cm	50	70% (35)	
>1 cm	91	76.9% (70)	
No. of brain metastases			0.907
1	33	72.7% (24)	
2–3	15	80% (12)	
>3	93	72.7% (69)	
dsGPA			0.821
0.5–1.5	97	75% (72)	
2–4	44	74.2% (33)	

By log-rank test. Abbreviations: WBRT: whole-brain radiation therapy; OS: overall survival; TKI: tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; dsGPA: disease-specific Graded Prognostic Assessment.

Table 3. Univariate and multivariate Cox regression analyses of covariables associated with OSm.

	Univariate Analyses		Multivariate Analyses	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
WBRT				
Yes vs. no	0.36 (0.25 to 0.53)	<0.001	0.34 (0.23 to 0.51)	<0.001
Age				
41–70 vs. ≦40	1.45 (0.46 to 4.58)	0.532		
>70 vs. ≦40	2.69 (0.82 to 8.81)	0.101		
Female vs. male	0.52 (0.36 to 0.75)	0.001	0.44 (0.25 to 0.75)	0.003
Initial Clinical stage				
III–IV vs. I–II	1.77 (0.72 to 4.35)	0.21		
Clinical T classification				
3–4 vs. 1–2	1.26 (0.84 to 1.91)	0.268		
Clinical N classification				
2–3 vs. 0–1	1.31 (0.9 to 1.92)	0.165		
Extracranial metastases				
Lung				
Yes vs. no	1.26 (0.88 to 1.8)	0.216		
Bone				
Yes vs. no	1.38 (0.89 to 2.13)	0.148		
Liver				
Yes vs. no	1.59 (1 to 2.51)	0.046		
Lung surgery				
Yes vs. no	0.5 (0.29 to 0.88)	0.016	0.47 (0.26 to 0.84)	0.01

Table 3. *Cont.*

	Univariate Analyses		Multivariate Analyses	
	HR (95%CI)	***p*-Value**	**HR (95%CI)**	***p*-Value**
Brain surgery				
Yes vs. no	0.5 (0.34 to 0.76)	0.001	0.64 (0.41 to 0.97)	0.037
Number of lines of systemic chemotherapy				
>2 vs. 0–2	1.13 (0.76 to 1.69)	0.534		
Number of lines of TKI				
>1 vs. 1	0.71 (0.49 to 1.03)	0.069		
ECOG				
1 vs. 0	0.93 (0.64 to 1.34)	0.693		
2 vs. 0	1.3 (0.59 to 2.84)	0.515		
Smoking				
Former or current vs. never	1.66 (1.11 to 2.48)	0.013	0.85 (0.48 to 1.53)	0.59
Symptomatic brain metastases				
Yes vs. no	0.91 (0.62 to 1.34)	0.639		
Size of largest brain tumor				
>1 cm vs. ≦1 cm	0.99 (0.68 to 1.45)	0.977		
No. of brain metastases				
2–3 vs. 1	1.25 (0.66 to 2.37)	0.5		
>3 vs. 1	1.44 (0.92 to 2.26)	0.109		
dsGPA				
0.5–1.5 vs. 2–4	1.41 (0.95 to 2.1)	0.089		

By Cox regression analyses. Abbreviations: OSm: overall survival time after the diagnosis of brain metastases; WBRT: whole-brain radiation therapy; TKI: tyrosine kinase inhibitor; ECOG: Eastern Cooperative Oncology Group; dsGPA: disease-specific Graded Prognostic Assessment.

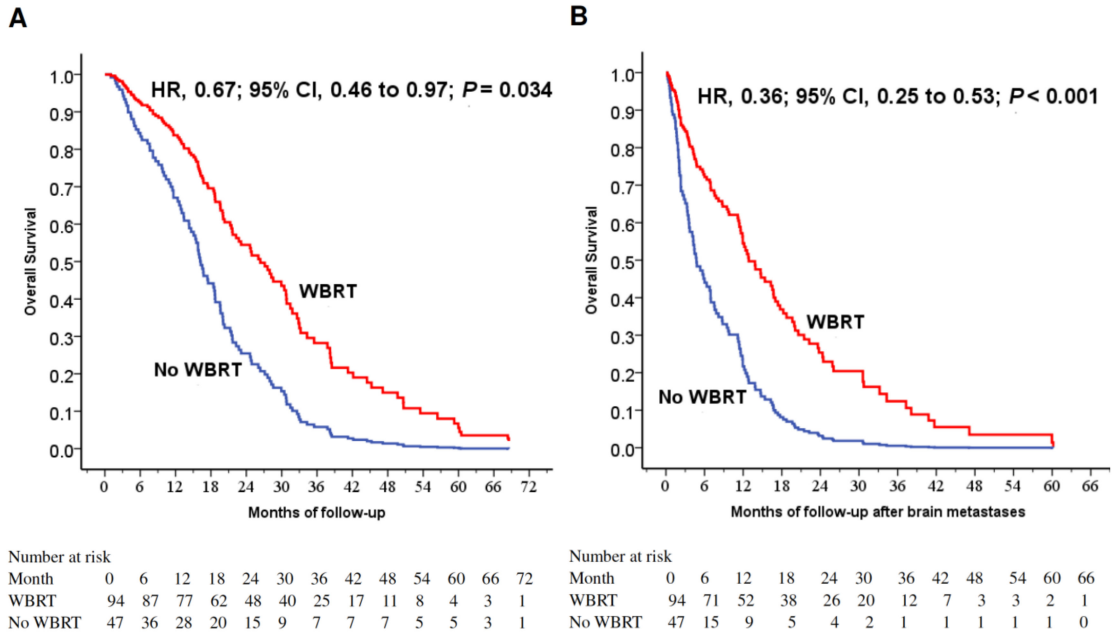
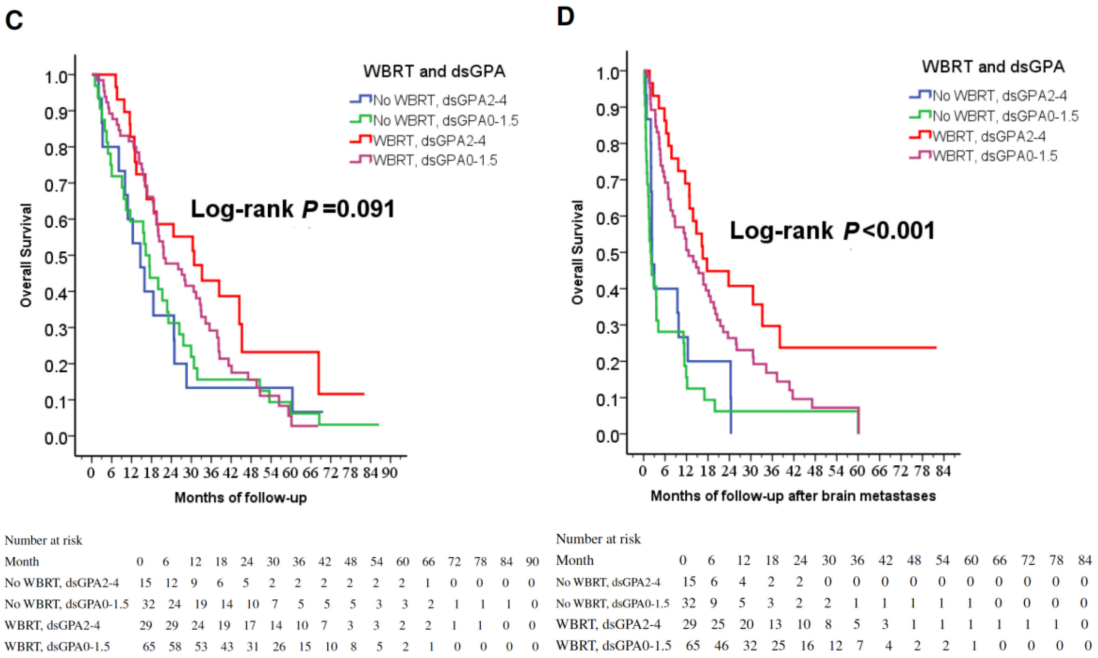


Figure 1. *Cont.*



Number at risk

Month	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90
No WBRT, dsGPA2-4	15	12	9	6	5	2	2	2	2	2	2	1	0	0	0	0
No WBRT, dsGPA0-1.5	32	24	19	14	10	7	5	5	5	3	3	2	1	1	1	0
WBRT, dsGPA2-4	29	29	24	19	17	14	10	7	3	3	2	2	1	1	0	0
WBRT, dsGPA0-1.5	65	58	53	43	31	26	15	10	8	5	2	1	0	0	0	0

Number at risk

Month	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
No WBRT, dsGPA2-4	15	6	4	2	2	0	0	0	0	0	0	0	0	0	0
No WBRT, dsGPA0-1.5	32	9	5	3	2	2	1	1	1	1	1	0	0	0	0
WBRT, dsGPA2-4	29	25	20	13	10	8	5	3	1	1	1	1	1	1	0
WBRT, dsGPA0-1.5	65	46	32	25	16	12	7	4	2	2	1	0	0	0	0

Figure 1. (**A**) Cox regression comparing overall survival in epidermal growth factor receptor-mutant non-small-cell lung cancer patients under tyrosine kinase inhibitors treated with and without WBRT. (**B**) Cox regression comparing overall survival time after the diagnosis of brain metastases in epidermal growth factor receptor-mutant non-small-cell lung cancer patients under tyrosine kinase inhibitors treated with and without WBRT. (**C**) Overall survival of patients stratified by WBRT and dsGPA score. (**D**) Overall survival after the diagnoses of brain metastases in patients stratified by WBRT and dsGPA score. Abbreviations: WBRT=whole-brain radiation therapy; dsGPA=disease-specific Graded Prognostic Assessment.

3.3. Subgroup Analyses

In identifying potential differences in the benefits of WBRT for patients by the dsGPA score, there was a trend toward improved OS in the group of TKI + WBRT ($p = 0.091$, Figure 1C); furthermore, WBRT significantly improved OSm regardless of dsGPA score ($p < 0.001$, Figure 1D), while the mean BM-free survival rates were similar in both groups (9.2 ± 13.6 months vs. 14.5 ± 17.8 months, $p = 0.312$). As a result, OSm caused survival difference, and longer OSm contribute to longer OS. WBRT was a strong favorable prognostic factor for longer survival.

4. Discussion

We now routinely use molecular selection to identify patients with NSCLC who would benefit from target therapy. The Bureau of National Health Insurance of Taiwan reimburses TKIs prescribed after a diagnosis of stage IIIB or IV lung cancer. Target therapies have resulted in major shifts in the treatment paradigm for lung cancer [30]. Fifteen years ago, Omuro et al. reported that the incidence of the central nervous system as an initial failure site reached 33% in EGFR-TKI responders with advanced NSCLC regardless of disease control in the lungs [31]. Intrinsic resistance of metastatic clones, incomplete TKI penetration of the BBB and longer survival are possible explanations for this high incidence [31]. One retrospective study in Taiwan reported that more patients with advanced EGFR-mutated NSCLC died of BMs than did those with wild-type (44.8% vs. 8.3%, $p < 0.001$) [32]. This change in the causes of death was noted after the era of EGFR-TKI treatment. The present study found that WBRT prolonged OS in patients with EGFR-mutated NSCLC who developed BM.

Xu et al. stated that aggressive local ablative therapy including surgery or RT to all metastatic sites improved OS compared with local ablative therapy to partial sites or observation alone [33].

Magnuson et al. performed a retrospective study on the topic of the optimal sequence of stereotactic radiosurgery, WBRT, and EGFR-TKIs in patients with EGFR-mutated NSCLC who developed BM. They reported that upfront brain RT resulted in longer OS compared with upfront EGFR-TKIs (stereotactic radiosurgery with 46 months versus WBRT with 30 months versus EGFR-TKI with 25 months, $p < 0.001$) [34]. Li et al. also confirmed the use of upfront WBRT for patients with EGFR-mutated NSCLC and multiple BM improved OS [35]. Although the timing of WBRT was not involved in the present study, we demonstrated worsened OS without WBRT and that WBRT contributed to the addition of approximately one year of survival after the diagnosis of BM.

However, Ke et al. reported no statistically significant difference in the OS between the First-line EGFR-TKI-alone group and First-line EGFR-TKI plus WBRT [36]. It is worth noting that first-generation EGFR-TKIs hardly penetrate across the BBB at the recommended doses [24]. In their study [36], the performance status, dsGPA, surgery to primary or metastatic sites were not documented, and these factors might affect OS. He et al. reported that concurrent EGFR-TKI and WBRT significantly improved the median intracranial progression-free survival compared with EGFR-TKI alone (17.7 vs. 11.0 months, $p = 0.015$); however, there was no significant OS difference (28.1 vs. 24.0 months, $p = 0.756$) [37]. In their study, they prescribed three types of different TKIs (erlotinib, gefitinib and icotinib) and 20 patients in the group of 48 patients who were given EGFR-TKI alone initially received salvage WBRT upon BM progression. This group was not purely without WBRT.

Lee et al. reported that EGFR-mutant NSCLC patients with BM who had received EGFR T790M inhibitors survived longer (41.1 vs. 19.8 months) [38]. Ng et al. found that one of the favorable prognostic factors was female gender (p <.001) in patients with NSCLC receiving WBRT [39]. In the present study, the median OSm was 14.3 months (95% CI, 9.5 to 18.3) in the TKI + WBRT group and 2.3 months (95% CI, 2 to 2.6) in the TKI alone group. On multivariate analysis, WBRT ($p < 0.001$) and female ($p = 0.003$) were associated with improved OS.

WBRT is associated with the risks of acute and late toxicities. Cognitive deficits attributed to RT were first reported in children treated for leukemia or brain tumors [40], and this bias was partly caused by greater susceptibility of the developing brain in youngsters [41]. BM by itself negatively affects cognitive function; additionally, baseline cognitive decline from aging in the cancer patients may also impact cognition [42]. Cognitive dysfunction can be caused by brain tumors, psychological distress, comorbidities such as vascular risk factors and diabetes, or by tumor-related epilepsy and its treatment (surgery, RT, anticonvulsants, chemotherapy, or corticosteroids) [40]. It can be difficult to differentiate from the effects of the tumor itself or RT complication [43]. Even though several recent publications have brought into question the role of WBRT and the possible risk of long-term neurotoxicity, WBRT curbed neurological decline [44]. A prospective study showed that the BBB permeability of gefitinib increased in accordance with escalated dose of WBRT [24]. An analysis from Radiation Therapy Oncology Group (RTOG) Study 91-04 showed that WBRT improved the scores on Mini-Mental State Examination in the patients with BM [45]. The optimization of WBRT with pharmacological and technical innovations to selectively spare organs involved in the memory process may decrease the potential long-term neurotoxicity [33].

At present, the treatment selection based on driver mutation status improves survival. Given the advancement of systemic therapy for extracranial lesions of metastatic NSCLC, patients now live long enough to develop BM [32]. WBRT, however, may be deferred and even omitted after the emergence of TKI by some clinicians. Based on prospective cohort studies, recently the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for metastatic NSCLC recommended the use of next-generation TKI for patients with a druggable oncogene driver (EGFR, ALK) and clinically asymptomatic BM [46]. Contradictory results were offered. Another retrospective study in North America reported that First-line WBRT for BM from EGFR/ALK-driven NSCLC was associated with longer time to intracranial progression than was radiosurgery or TKI alone [47]. For patients with ECOG 0-2 in the present study, the absence of WBRT was detrimental to their survival. In terms of

different subgroups, even those with favorable dsGPA scores had survival benefit from the addition of WBRT compared with TKI alone.

The results of this study should be interpreted with caution, owing to the heterogeneity of patient characteristics and possible intrinsic bias related to the retrospective design. We intended to minimize bias by using multivariate analyses. There were some pitfalls of the present study. Firstly, radiosurgery was in general not used due to the regulations of National Health Insurance reimbursement. Secondly, we used OS rate to measure the clinical benefits, which might not represent the tumor response. Thirdly, cognitive evaluation was not fully documented. The precise roles of WBRT need to be validated in a randomized control trial. Moreover, Osimertinib is a third-generation EGFR-TKI developed specifically to treat patients with T790M mutation, and only 3.5% of the patients in the study cohort used Osimertinib.

5. Conclusions

The present study suggested that WBRT significantly prolonged OS in patients with EGFR-mutated NSCLC who developed BM. The combination of WBRT and TKI improved OS compared with TKI alone. To the best of our knowledge, this study is the first to demonstrate the negative survival impact from the omission of WBRT in patients with targetable driver mutation. A longer follow-up studying the role of multi-modality treatment in EGFR-mutated NSCLC with BM is urgently warranted.

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