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Does lung cancer mutation status and targeted therapy predict for outcomes and local control in the setting of brain metastases treated with radiation?

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Background. We investigated effects of genetic alterations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and Kirsten rat sarcoma viral oncogene homolog (KRAS) on overall survival (OS) and local control after stereotactic radiosurgery for brain metastases in non–small cell lung cancer (NSCLC).

Methods. A cohort of 89 out of 262 NSCLC patients (2003–2013) treated with gamma knife radiosurgery for brain metastases had genotyping available and were selected as our study population.

Results. Median follow-up was 12 months. Median OS rates for the EGFR, KRAS, echinoderm microtubule-associated protein-like 4 (EML4)–ALK mutated, and wild-type cohorts were 17, 7, 27, and 12 months, respectively ($P = .019$), and for targeted versus non-targeted therapy 21 and 11 months, respectively ($P = .071$). Targeted therapy was a strong predictor of increased OS on univariate ($P = .037$) and multivariate ($P = .022$) analysis. Gender, primary tumor controlled status, recursive partitioning analysis class, and graded prognostic assessment score were associated with OS ($P < .05$). On multivariate analysis, positive EGFR mutational status was a highly significant predictor for decreased survival (hazard ratio: 8.2; 95% CI: 2.0–33.7; $P = .003$). However, when we recategorized EGFR-mutant cases based on whether they received tyrosine kinase inhibitor, OS was no longer significantly shorter (hazard ratio: 1.5; $P = .471$). Median OS for patients with and without local failure was 17 and 12 months, respectively ($P = .577$). Local failure rates for EGFR, KRAS, EML4-ALK mutated, and wild-type cohorts by lesion were 8.7%, 5.4%, 4.3%, and 5.1%, respectively.

Conclusions. This study suggests that EGFR tyrosine kinase mutation and ALK translocation results in improved survival to targeted therapies and that mutation status itself does not predict survival and local control in patients with brain metastases from NSCLC.

Keywords: brain metastases, mutations, non-small cell lung cancer, stereotactic radiosurgery, targeted therapy.

Non–small cell lung cancer (NSCLC) accounts for ~85% of all lung cancers.[1] Additionally, lung cancer continues to be the most common cause of cancer-related deaths worldwide, with a 5-year survival rate of <20% in patients in the United States (http://seer.cancer.gov). In the last decade, NSCLC management has advanced toward the stratification of patients based on the presence of key, actionable genetic alterations, with epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, and echinoderm microtubule-associated protein-like 4 (EML4)–anaplastic lymphoma kinase (ALK) gene translocations as the 3 largest groups.[2–5] The development of targeted therapy with tyrosine kinase inhibitors (TKIs) has led to improved outcomes for patients with EGFR mutations or ALK rearrangements.[6,7]

Brain metastases (BM) are a common complication in NSCLC patients. Approximately 20% to 40% of patients with NSCLC

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develop BM during the course of their illness, and this is associated with a poor life expectancy.[8–11] Survival rates can range from 2 months if treated with steroids alone to 14 months if treated with a combination of stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), and/or neurosurgical resection (NSG).[12,13] One possible explanation for this variability in outcomes is the molecular heterogeneity of NSCLC, with BM behaving differently depending on the presence or absence of these known mutations. Recent studies have suggested that positive EGFR mutation status in NSCLC patients with BM is associated with increased radiosensitivity relative to other mutations, including KRAS.[14,15] Other studies have reported that EGFR mutation status in NSCLC patients with BM predicted for treatment response to targeted therapies such as erlotinib.[16,17]

The purpose of our study was to determine whether EGFR, KRAS, or EML4-ALK mutation status predicted for overall survival (OS) and local control in NSCLC patients treated with SRS for BM at our institution. Furthermore, we sought to evaluate whether targeted therapies independently predicted for SRS BM survival response rates in these patients.

Methods

From July 2003 to August 2013, we evaluated 262 consecutive patients with NSCLC treated with gamma knife radiosurgery for BM at Columbia University Medical Center. A cohort of 89 out of 262 patients had genotyping available and were selected as our study population. The following variables of potential prognostic significance were captured from medical records: age (as a continuous variable at initial diagnosis of BM), race (Caucasian vs non-Caucasian), gender, histology, status of primary tumor (controlled vs not controlled), type of initial and salvage treatment of BM (surgery, gamma knife radiosurgery, WBRT), mutation status (EGFR, KRAS, EML4-ALK, or wild type [WT]), treatment for lung cancer (targeted vs nontargeted), number of BM, and extracranial metastases (present vs not present). Local and distant brain failures were assessed by reviewing follow-up brain imaging studies and were classified according to Response Evaluation Criteria in Solid Tumors. In-field local failure was defined by a $\geq$20% increase in the longest diameter of the lesion over nadir. Distant brain failure was defined as a new brain lesion detected on follow-up MRI that was not previously treated or present on prior gamma knife treatment-planning MRIs. Half of the patients ($n = 45$) presented with a synchronous diagnosis of brain metastasis along with or within 2 months of their NSCLC. Forty-four patients were diagnosed with metachronous brain metastasis, which was defined as brain metastasis diagnosed at >2 months after the primary lung tumor.[18,19] We calculated the recursive partitioning analysis (RPA) class: class I included patients of age <65 years, KPS score $\geq$70, controlled primary tumor, and no extracranial metastases; class III included all patients with a KPS score <70; and class II comprised those not included in class I or III.[10] Graded prognostic assessment (GPA) scores 0–4 were also calculated for all patients based on age <50 years (1 point), 50–59 years (0.5 points), or >60 years (0 points); KPS stratified by <70 (0 points), 70–80 (0.5 points), or >90 (1 point); number of BM stratified by 1 (1 point), 2–3 (0.5 points), or >3 (0 points); and presence or absence of extracranial metastases (0 or 1 point, respectively).[13,20] Patients were stratified based on mutation status into 4 groups: EGFR, KRAS, EML4-ALK, or WT. Genotyping for NSCLC was performed at Columbia University Medical Center as a part of routine care. EGFR mutation status was detected by analyzing the EGFR kinase domain (exons 18–21) by polymerase chain reaction and capillary gel electrophoresis. KRAS mutation was detected by using the KRAS codon 12/13 amplification refractory mutation system–Scorpions assay and included G12–34G, G12–35G. ALK rearrangements were identified by fluorescence in situ hybridization (Vysis LSI ALK [2p23] Dual Color, Break Apart Rearrangement Probe, Abbott Molecular). Overall survival was calculated from the start day of the first treatment received for BM. Patients were excluded if they had incomplete information, including date and types of treatments or missing dates of death or last follow-up. The study was approved by the institutional review board of Columbia University Medical Center.

Statistical Analysis

For baseline variables, summary statistics were constructed by use of frequencies and proportions for categorical data and with medians and standard deviation for continuous variables. To determine significant differences between baseline characteristics, a chi-square test and one-way ANOVA were used for categorical and continuous variables, respectively. For categorical variables, column proportions were compared and *P*-values adjusted using the Bonferroni method at the .05 level. Survival curves were calculated using the Kaplan–Meier method and Cox proportional hazards model. Log-rank, Breslow, and Tarone–Ware tests were used to assess significant survival differences between groups. Patients lost to follow-up were censored for survival as of the last visit. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by the Cox proportional hazards model. To identify baseline and clinical variables associated with OS time, multivariate analysis was performed with the Cox proportional hazards model. $P < .05$ was considered statistically significant. Analysis was performed using IBM SPSS version 20.

Results

Eighty-nine patients (43 female) were included in the analysis, with a median age of 63 years (range, 35–89). Median follow-up was 12 months for all patients and the same for local control. No major difference in baseline characteristics was identified for this population, with the exception of a small group of KRAS-positive patients ($n = 10$ [83.3%]) receiving SRS alone (Table 1). Nineteen (21.3%) had EGFR mutation, 12 (13.5%) had KRAS mutation, 6 (6.7%) had EML4-ALK translocation, and 52 (58.4%) had no mutation. Of the EGFR-mutant tumors, 8 had exon-19 deletions, 4 had exon-21 L858R missense mutation, 1 had an exon-18 point mutation, 1 had an exon-19 deletion and T790M mutation, and 1 had an exon-18 point mutation and exon-20 insertion mutation (p.S768I). Specific EGFR mutation was not documented in the rest of the patients. Histology included 79 adenocarcinoma (88.8%) and 10 squamous cell/large cell carcinoma (11.2%). Study population was categorized into RPA class I = 8 (9%); class II = 70 (78.7%); and class III = 11 (12.3%). GPA scores

Table 1. Baseline characteristics

	EGFR Mutant	KRAS Mutant	ALK Translocation	Wild Type	*P*
Number of patients	19	12	6	52	
Age	59	64	55	63	.078
SD	14.547	12.985	11.444	9.701	
Gender					
F	14_a (73.7%)	6_a (50.0%)	2_a (33.3%)	21_a (40.4%)	.080
Race					
White	11_a (57.9%)	10_a (83.3%)	4_a (66.7%)	31_a (59.6%)	.453
Histology					
Adenocarcinoma	19_a (100.0%)	12_a (100.0%)	6_a (100.0%)	42_a (80.8%)	.046
Targeted therapy					
Yes	15_a (78.9%)	0_b (0.0%)	5_a (83.3%)	0_b (0.0%)	.001
No	4_a (21.1%)	12_b (100.0%)	1_a (16.7%)	52_b (100.0%)	
Number of BM					
One	10_a (52.6%)	4_a (33.3%)	2_a (33.3%)	22_a (42.3%)	.702
Multiple	9_a (47.4%)	8_a (66.7%)	4_a (66.7%)	30_a (57.7%)	
Extracranial metastases					
No	3_a (15.8%)	0_a (0.0%)	1_a (16.7%)	12_a (23.1%)	.306
Yes	16_a (84.2%)	12_a (100.0%)	5_a (83.3%)	40_a (76.9%)	
Primary tumor status					
Controlled	9_a (47.4%)	8_a (66.7%)	6_a (100.0%)	27_a (51.9%)	.102
Uncontrolled	10_a (52.6%)	4_a (33.3%)	0_a (0.0%)	25_a (48.1%)	
RPA class					
I	0_a (0.0%)	0_a (0.0%)	1_a (16.7%)	7_a (13.5%)	.310
II	17_a (89.5%)	9_a (75.0%)	5_a (83.3%)	39_a (75.0%)	
III	2_a (10.5%)	3_a (25.0%)	0_a (0.0%)	6_a (11.5%)	
GPA score					
0–1	2_a (10.5%)	1_a (8.3%)	0_a (0.0%)	5_a (9.6%)	.079
1.5–2.5	8_a (42.1%)	8_a (66.7%)	4_a (66.7%)	39_a (75.0%)	
3	4_a (21.1%)	3_a (25.0%)	0_a (0.0%)	5_a (9.6%)	
3.5–4	5_a (26.3%)	0_a (0.0%)	2_a (33.3%)	3_a (5.8%)	
Patients status					
Alive	7_a (36.8%)	6_a (50.0%)	5_a (83.3%)	20_a (38.5%)	.175
Deceased	12_a (63.2%)	6_a (50.0%)	1_a (16.7%)	32_a (61.5%)	
Treatment modalities					
SRS	$7_{a,\ b}$ (36.8%)	10_b (83.3%)	$3_{a,\ b}$ (50.0%)	21_a (40.4%)	.027
SRS + WBRT	5_a (26.3%)	0_a (0.0%)	0_a (0.0%)	6_a (11.5%)	
SRS + NSG	2_a (10.5%)	2_a (16.7%)	3_a (50.0%)	18_a (34.6%)	
SRS + WBRT + NSG	5_a (26.3%)	0_a (0.0%)	0_a (0.0%)	7_a (13.5%)	

Bonferroni correction. Each subscript letter (a or b) denotes a subset of mutation categories whose column proportions do not differ significantly from each other at the .05 level.

of 0–1, 1.5–2.5, 3.0, and 3.5–4.0 were determined for all patients. Forty-one patients received SRS only, 11 patients underwent SRS + WBRT, 25 received SRS + NSG, and 12 received all 3 treatment modalities. Twenty patients (23.5%) received targeted therapy, including erlotinib ($n = 13$), crizotinib ($n = 5$), and afatinib ($n = 2$). Median OS for the EGFR, KRAS, EML4-ALK mutated, and WT cohorts was 17, 7, 27, and 12 months, respectively ($P = .019$) (Fig. 1). Median OS for the targeted and nontargeted therapy groups was 21 and 11 months, respectively (Table 2).

On univariate analysis (Supplementary Table S1), targeted therapy was a strong predictor of increased OS (HR: 0.5; 95% CI: 0.2–0.9; $P = .037$). Age, gender, primary tumor histology, EML4-ALK status, primary tumor controlled status, RPA class, and GPA score were also significant predictors for OS ($P < .05$). Extracranial metastases were not statistically significant (HR: 1.5; 95% CI: 0.7–3.2; $P = .261$). Race and number of BM were not significant predictors. One versus multiple BM was not significant for OS (HR: 1.2; 95% CI: 0.7–2.1; $P = .513$). There was no significant difference in median OS between patients with one or multiple BM (25 vs 22 mo, respectively). There was also no significant difference in survival between patients with synchronous versus metachronous diagnosis of BM ($P = .606$). Fifty-seven patients had follow-up MRI available to

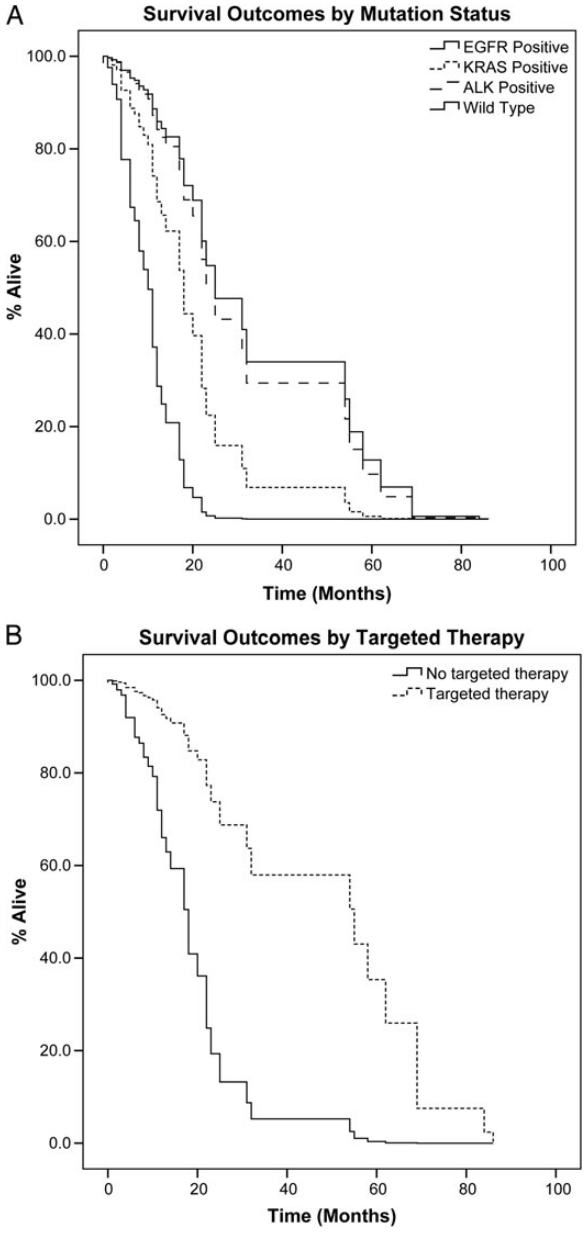

Fig. 1. Multivariate Cox regression analysis: (A) survival outcomes stratified by mutation status; (B) targeted therapy shows a significant increase in survival.

determine local and distant brain failures. When analyzed, both of these variables were not statistically significant for survival (Table 3). Median OS for patients with and without local failure was 17 and 12 months, respectively ($P = .577$). Local failures for EGFR, KRAS, EML4-ALK mutated, and WT cohorts by lesion were 8.7%, 5.4%, 4.3%, and 5.1%, respectively (Table 3).

Based on these univariate results, age, gender, histology, primary tumor controlled status, RPA class, GPA score, targeted therapy, and mutation status were included in the multivariate Cox proportional hazards model. On multivariate analysis, use of targeted therapy was a strong predictor of increased OS

Table 2. Survival outcomes by mutation status, targeted therapy, and local control

	Median Survival	95% CI	*P*
EGFR positive[a]	17	10–25	.019
KRAS positive	7	3–11	
ALK translocation	27	17–73	
Wild type	12	7–17	
No targeted therapy	11	8–15	.071
Targeted therapy	21	11–27	
Local failure	17	7–27	
No local failure	12	10–17	.577

[a]Of the EGFR-mutant tumors, 8 had exon-19 deletions, 4 had exon-21 L858R missense mutation, 1 had an exon-18 point mutation, 1 had an exon-19 deletion and T790M mutation, and 1 had an exon-18 point mutation and exon-20 insertion mutation (p.S768I). Specific EGFR mutation was not documented in the rest of the patients.

(HR: 0.2; 95% CI: 0.04–0.78; $P = .022$). Gender, primary tumor controlled status, RPA class, and GPA score were significant predictors for OS ($P < .05$). Primary tumor histology showed a trend toward increased OS in adenocarcinoma ($P = .067$) (Table 4). On multivariate analysis, positive EGFR mutational status was a significant predictor for decreased survival (HR: 8.2; 95% CI: 2.0–33.7; $P = .003$). In order to confirm this finding, we repeated the multivariate analysis by categorizing EGFR-mutant patients into 2 groups—group 1 included 15 EGFR-mutant patients who received TKI, and group 2 included 4 EGFR-mutant patients who received only chemotherapy. Results indicated that EGFR mutational status was no longer a significant predictor of survival (HR: 1.5; 95% CI: 0.5–4.2; $P = .471$). Positive KRAS mutational status also showed a trend toward decreased OS (HR: 2.5; 95% CI: 0.8–7.3) but did not reach significance ($P = .101$).

Discussion

BM are the most common malignancy of the central nervous system, with NSCLC representing the most common primary tumor associated with BM. Given that somatic gene mutations can be detected in up to 60% of NSCLC patients,[21] we sought to investigate whether these mutations were predictive of survival and local control in NSCLC patients with BM treated with SRS.

We found that patients with an EGFR mutation had a significantly increased risk for death compared with patients with WT tumors on multivariate analysis (HR: 8.2, $P = .003$). We believe that this is a false positive result given that after correcting for patients who received TKI, EGFR was no longer a significant risk for death.[22–24] A trend toward poor survival was seen in patients with KRAS mutations, but this did not reach statistical significance (HR: 2.5, $P = .101$). We also found that patients with an ALK gene rearrangement showed improved survival on univariate analysis ($P = .044$).

There have been conflicting reports regarding the effect of EGFR mutation status on survival in NSCLC patients with BM. Eichler and colleagues[22] reported that in 93 NSCLC patients with BM, EGFR mutation status was independently associated with improved survival on multivariate analysis. Median survival

Table 3. Local failure by mutation status and tyrosine kinase–activated tumors versus other tumors

	EGFR Mutant	ALK Translocation	KRAS Mutant	Wild Type
By patient (in-field)	5/11 (45.5%)	1/6 (16.7%)	2/9 (22.2%)	4/31 (12.9%)
Distant brain	4/11 (36.4%)	3/6 (50%)	4/9 (44.4%)	12/31 (38.7%)
By lesion (in-field)	6/69 (8.7%)	1/23 (4.3%)	2/37 (5.4%)	4/77 (5.1%)
	Tyrosine kinase– activated tumors	Other	*P*	
By patient (in-field)	6/17 (35.2%)	6/40 (15%)	.154	
Distant brain	7/17 (41.1%)	16/40 (40%)	.940	
By lesion (in-field)	7/92 (7.6%)	6/114 (5.2%)	.079	

In-field local failure was defined by a ≥20% increase in the longest diameter of the lesion over nadir. Distant brain failure was defined as a new brain lesion detected on follow-up MRI that was not previously treated or present on prior gamma knife treatment-planning MRIs.

from time of BM diagnosis in EGFR-mutant patients was 14.5 months versus 7.6 months in EGFR WT patients. In this study 78% of patients with EGFR mutation received TKI after BM diagnosis, while ∼20% of patients with EGFR WT received TKI, potentially confounding the results. Another contributing factor may be the poor survival seen in the WT patients (7.6 mo vs 12 mo in our cohort), thereby exaggerating the survival benefit seen in EGFR-mutant patients.

Targeted therapy with TKIs has been reported to improve the outcome of BM patients with NSCLC.[25,26] A recent study from China reported the efficacy of TKI in EGFR-mutant patients with BM associated with NSCLC.[23] In 109 patients, half of whom had positive EGFR mutations, administration of TKI significantly improved OS independently of EGFR mutation status. The median survival in patients who received TKI was 31.9 months compared with 17.0 months in the non-TKI group. This is consistent with our finding that patients who received targeted therapy had a median survival of 21 months compared with 11 months for patients who did not ($P = .071$). On multivariate analysis, we found the use of targeted therapy to be significant for improved survival. A similar finding by Mak et al[24] reported that patients with EGFR mutation or ALK rearrangements had significantly worse outcome if they were not on TKI therapy; median survival was 19.6 months and 9.0 months with and without TKI, respectively.

Regarding local and regional control of BM treated with SRS, we found that local and intracranial control were not statistically different among EGFR, ALK, KRAS, and WT patients. This finding is in contrast to a study by Johung et al,[15] who evaluated local and distant brain control for NSCLC BM treated with SRS stratified by mutation status. Seventy-nine patients with available molecular status and follow-up imaging were analyzed. With a median follow-up of 6.2 months, they reported that patients with EGFR and ALK mutant status had 100% local control rates, whereas KRAS-mutant and WT patients had local control rates of 82% and 81%, respectively. Distant brain failure was 43% in EGFR-mutant, 78% in ALK-mutant, 59% in KRAS-mutant, and 41% in WT patients. Overall survival was not reported. The authors concluded that EGFR- and ALK-mutant patients had more radiosensitive tumors. In contrast to their perfect local control rates, we found that patients with EGFR and ALK mutant status did in fact develop local failure despite SRS. One explanation for this is our longer

Table 4. Multivariate analysis for OS

	P	HR	95% CI	
			Lower	Upper
Age	.798	1.01	0.97	1.05
Male gender	.001	3.7	1.7	8.1
Adenocarcinoma	.067	0.3	0.1	1.1
Mutation status				
Wild type	Reference category			
EGFR positive	.003	8.2*	2.0	33.7
KRAS positive	.101	2.5	0.8	7.3
ALK translocation	.917	1.1	0.11	12.0
Targeted therapy	.022	0.2	0.04	0.78
Primary tumor status Not controlled	.022	2.8	1.2	6.7
RPA class				
Class III	Reference category			
Class I	.002	0.05	0.01	0.33
Class II	.033	0.4	0.2	0.9
GPA score				
1	Reference category			
2	<.001	0.05	0.02	0.14
3	<.001	0.05	0.01	0.20
4	<.001	0.01	0.001	0.070
Treatment modalities				
SRS	Reference category			
SRS + WBRT	.150	0.5	0.2	1.3
SRS + NSG	.004	0.3	0.1	0.7
SRS + WBRT + NSG	<.001	0.1	0.03	0.32
*Multivariate analysis in EGFR subgroups				
Wild type	Reference category			
EGFR mutant positive + chemotherapy only	.005	7.5	1.9	30.4
EGFR mutant positive + TKI	.471	1.5	0.5	4.2

Abbreviations: EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog mutations; ALK, anaplastic lymphoma kinase gene translocations; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; NSG, neurosurgical resection; CI, confidence interval; TKI, tyrosine kinase inhibitor.

follow-up time of 12 months compared with 6 months in their study.

This study has several limitations, including its retrospective nature, which opens the possibility of unforeseen variables and biases. Another limitation is that most patients did not undergo resection, precluding confirmation that BM lesions harbored the same mutation status as the primary cancer. The repeat multivariate analysis, done after further dividing the EGFR population, resulted in groups with a low *n*, which makes it difficult to draw the conclusions. Our sample size was limited by the substantial number of NSCLC patients who did not undergo genotyping. However, this cohort represents the entire NSCLC patient population that received SRS for BM at our institution. Despite these limitations, our study provides some insight into potential trial designs for future prospective studies, and we had sufficient power to perform multivariate analyses adjusted for many potential confounders. We believe that future prospective studies for lung cancer patients with BM treated with radiation should include collection of time to disease progression and quality of life data, as we did not routinely collect them. Furthermore, we are in the process of designing a test program for patients with newly diagnosed BM from NSCLC at our institution with the goal of allowing the use of adequate TKIs to treat BM as effectively as possible.

Conclusion

In the setting of SRS for NSCLC BM patients, our results suggest that EGFR tyrosine kinase mutant and ALK translocation tumors respond well to targeted therapies, whereas EGFR mutation status itself does not predict survival. Positive KRAS mutation status for NSCLC patients with BM trended but was not significant for decreased OS. Positive ALK mutation status trended for improved OS but lacked enough sample size to detect significance. There was no difference in local failure rate by mutation status.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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References

1. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med*. 2008;359(13):1367–1380.
2. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304(5676):1497–1500.
3. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. *N Engl J Med*. 1990;323(9):561–565.
4. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448(7153):561–566.
5. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004; 350(21):2129–2139.
6. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst*. 2013;105(9): 595–605.
7. Antoniu SA. Crizotinib for EML4-ALK positive lung adenocarcinoma: a hope for the advanced disease? Evaluation of Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363(18):1693–703. *Expert Opin Ther Targets*. 2011;15(3):351–353.
8. Sorensen JB, Hansen HH, Hansen M, et al. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. *J Clin Oncol*. 1988;6(9):1474–1480.
9. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. 2004;22(14):2865–2872.
10. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37(4):745–751.
11. Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol*. 2003;21(13):2529–2536.
12. Bhangoo SS, Linskey ME, Kalkanis SN. Evidence-based guidelines for the management of brain metastases. *Neurosurg Clin N Am*. 2011;22(1):97–104, viii.
13. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys*. 2010;77(3):655–661.
14. Hsiao SH, Lin HC, Chou YT, et al. Impact of epidermal growth factor receptor mutations on intracranial treatment response and survival after brain metastases in lung adenocarcinoma patients. *Lung Cancer*. 2013;81(3):455–461.
15. Johung KL, Yao X, Li F, et al. A clinical model for identifying radiosensitive tumor genotypes in non-small cell lung cancer. *Clin Cancer Res*. 2013;19(19):5523–5532.

16. Grommes C, Oxnard GR, Kris MG, et al. Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. *Neuro Oncol*. 2011;13(12): 1364–1369.
17. Jamal-Hanjani M, Spicer J. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain. *Clin Cancer Res*. 2012;18(4):938–944.
18. Getman V, Devyatko E, Dunkler D, et al. Prognosis of patients with non-small cell lung cancer with isolated brain metastases undergoing combined surgical treatment. *Eur J Cardiothorac Surg*. 2004;25(6):1107–1113.
19. Arrieta O, Villarreal-Garza C, Zamora J, et al. Long-term survival in patients with non-small cell lung cancer and synchronous brain metastasis treated with whole-brain radiotherapy and thoracic chemoradiation. *Radiat Oncol*. 2011;6:166.
20. Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys*. 2008;70(2): 510–514.
21. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009; 361(10):947–957.
22. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. *Neuro Oncol*. 2010;12(11):1193–1199.
23. Cai L, Zhu JF, Zhang XW, et al. A comparative analysis of EGFR mutation status in association with the efficacy of TKI in combination with WBRT/SRS/surgery plus chemotherapy in brain metastasis from non-small cell lung cancer. *J Neurooncol*. 2014; 120:423–430.
24. Mak KS, Gainor JF, Niemierko A, et al. Significance of targeted therapy and genetic alterations in EGFR, ALK, or KRAS on survival in patients with non-small cell lung cancer treated with radiotherapy for brain metastases. *Neuro Oncol*. 2014;16:296–302.
25. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. *Ann Oncol*. 2004;15(7):1042–1047.
26. Cappuzzo F, Calandri C, Bartolini S, et al. ZD 1839 in patients with brain metastases from non-small-cell lung cancer (NSCLC): report of four cases. *Br J Cancer*. 2003;89(2):246–247.