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ORIGINAL REPORT

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

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ABSTRACT

Purpose
Stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT), and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are treatment options for brain metastases in patients with EGFR-mutant non–small-cell lung cancer (NSCLC). This multi-institutional analysis sought to determine the optimal management of patients with EGFR-mutant NSCLC who develop brain metastases and have not received EGFR-TKI.

Materials and Methods
A total of 351 patients from six institutions with EGFR-mutant NSCLC developed brain metastases and met inclusion criteria for the study. Exclusion criteria included prior EGFR-TKI use, EGFR-TKI resistance mutation, failure to receive EGFR-TKI after WBRT/SRS, or insufficient follow-up. Patients were treated with SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI, or EGFR-TKI followed by SRS or WBRT at intracranial progression. Overall survival (OS) and intracranial progression-free survival were measured from the date of brain metastases.

Results
The median OS for the SRS (n = 100), WBRT (n = 120), and EGFR-TKI (n = 131) cohorts was 46, 30, and 25 months, respectively ($P < .001$). On multivariable analysis, SRS versus EGFR-TKI, WBRT versus EGFR-TKI, age, performance status, *EGFR* exon 19 mutation, and absence of extracranial metastases were associated with improved OS. Although the SRS and EGFR-TKI cohorts shared similar prognostic features, the WBRT cohort was more likely to have a less favorable prognosis ($P = .001$).

Conclusion
This multi-institutional analysis demonstrated that the use of upfront EGFR-TKI, and deferral of radiotherapy, is associated with inferior OS in patients with EGFR-mutant NSCLC who develop brain metastases. SRS followed by EGFR-TKI resulted in the longest OS and allowed patients to avoid the potential neurocognitive sequelae of WBRT. A prospective, multi-institutional randomized trial of SRS followed by EGFR-TKI versus EGFR-TKI followed by SRS at intracranial progression is urgently needed.

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INTRODUCTION

In 2015, an estimated 158,040 people in the United States died as a result of lung cancer, more than breast, colon, and prostate cancer combined.[1] As many as 40% of patients diagnosed with non–small-cell lung cancer (NSCLC) will develop brain metastases during the course of their disease, and this risk may be even greater in those who harbor an epidermal growth factor receptor (EGFR) mutation.[2,3] Activating mutations of the EGFR kinase domain are present in 10% to 15% of patients with lung adenocarcinoma in North America and up to 60% of patients in Asia.[4] Patients with EGFR-mutant NSCLC may have a higher likelihood of being diagnosed with brain metastases because of prolonged survival from targeted systemic agents and the increased quality of CNS imaging.[5,6] Before the development of targeted therapy, the median overall survival (OS) of an unselected

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population of EGFR-mutant and non–EGFR-mutant NSCLC patients with brain metastases ranged from 3 to 15 months.[7] However, in the current era of targeted therapy and immunotherapy, median OS after brain metastases of 19 to 58 months in patients with EGFR-mutant NSCLC has been observed.[8,9]

The first-line treatment of patients with advanced, recurrent, or metastatic NSCLC harboring an EGFR mutation is an EGFR–tyrosine kinase inhibitor (TKI).[10] Historically, brain metastases have been treated with surgical resection, stereotactic radiosurgery (SRS), or whole-brain radiotherapy (WBRT), either alone or in combination. More recently, phase II trials evaluating the use of erlotinib (an EGFR-TKI) alone for the treatment of brain metastases in patients naïve to EGFR-TKI therapy have reported median OS after brain metastases of 15.9 to 22.9 months, median progression-free survival (PFS) of 5.8 to 14.5 months, and CNS objective response rate of 55% to 89%.[11-14] In addition to avoiding a delay in the initiation of systemic therapy (as may be required with surgical resection, SRS, or WBRT), the use of upfront EGFR-TKI may also allow for the deferment or complete avoidance of metastasis-directed therapy and the resultant toxicity that may ensue. Therefore, there has been tremendous interest in assessing the effectiveness of upfront EGFR-TKI and withholding local therapies until progression of intracranial disease.

Although numerous phase II trials have investigated the efficacy of upfront EGFR-TKI for brain metastases, randomized data evaluating EGFR-TKI followed by SRS or WBRT at intracranial progression versus SRS or WBRT followed by EGFR-TKI are not available. Therefore, we conducted a pooled, multi-institutional analysis to determine the optimal management of patients with EGFR-mutant NSCLC who developed brain metastases and had not received EGFR-TKI.

MATERIALS AND METHODS

After approval by the Yale Human Investigation Committee, patient information was gathered from six academic centers under distinct institutional review board–approved protocols. All patients with EGFR-mutant lung adenocarcinoma who developed brain metastases between January 1, 2008, and December 31, 2014, were identified. Because the aim of the study was to evaluate TKI-naïve patients with newly diagnosed brain metastases, patients were excluded if they had prior EGFR-TKI use, had EGFR-TKI resistance mutation, failed to receive EGFR-TKI after WBRT or SRS, failed to receive radiotherapy (RT) after intracranial progression on EGFR-TKI, or were missing covariable data or < 6 months of follow-up. To remove a potentially confounding variable, patients who underwent surgical resection at the time of initial brain metastases were also excluded. Patients were treated with SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI, or EGFR-TKI followed by SRS or WBRT at intracranial progression.

The following variables were gathered for the analysis: age, sex, stage, smoking history, EGFR mutation, Eastern Cooperative Oncology Group (ECOG) performance status at the time of brain metastases, number of brain metastases, size of largest brain metastasis, whether the patient was symptomatic from brain metastases, type of RT delivered, name of EGFR-TKI, and name of systemic therapy after progressing on EGFR-TKI. Systemic disease status was assessed by the presence or absence of extracranial metastases at the time of brain metastases. The site of first progression after brain metastases (intracranial, extracranial, or concurrent) was identified. The date of initial cancer diagnosis, brain metastases diagnosis, intracranial progression, RT treatments, systemic therapy treatments, most recent follow-up, and death were recorded. Finally, a disease-specific Graded Prognostic Assessment (ds-GPA) was calculated for each patient to determine whether the cohorts shared similar prognostic features.

Magnetic resonance imaging scans of the brain, along with positron emission tomography–computed tomography(CT) and CT scans of the chest, abdomen, and pelvis, were reviewed per institutional standards to ascertain intracranial and extracranial disease status. Intracranial disease progression was distinguished from pseudoprogression using dynamic contrast imaging, diffusion imaging, magnetic resonance spectroscopy, positron emission tomography–CT of the brain, and surgical resection, either alone or in combination. Molecular pathology for EGFR activating mutations in the kinase domain was evaluated by polymerase chain reaction amplification at all six institutions. Three institutions assessed for activating mutations on exons 18 to 21, and three institutions assessed for activating mutations arising from a deletion on exon 19 (E746_A750) or a point mutation on exon 21 (L858R).

Characteristics of patients in the three groups were compared both descriptively and with the χ^2 test for categorical variables and analysis of variance for continuous variables. Kaplan-Meier analysis was used to estimate OS and intracranial PFS, whereas log-rank testing was used to assess for differences. OS was calculated from the date of brain metastases diagnosis until the date of death. Intracranial PFS was calculated from the data of brain metastases diagnosis until the date of growth of a previous lesion or the development of a new lesion. Univariable and multivariable Cox proportional hazards analysis examined factors associated with increased risk of death. For analysis of intracranial progression, a univariable and multivariable stepwise competing risks regression with forward selection was conducted with the primary end point of intracranial progression (local or distant), in the context of the competing risk of death.[15] Cumulative incidence curves were then generated for intracranial recurrence for patients who received EGFR-TKI first, SRS first, or WBRT first. Statistical analyses were performed using STATA 13.1 (Stata, College Station, TX).

RESULTS

After applying the aforementioned exclusionary criteria, 351 patients from six intuitions were identified. Of the 351 patients, 131 (37%) received EGFR-TKI followed by SRS or WBRT at intracranial progression, 120 (34%) were treated with WBRT followed by EGFR-TKI, and 100 (29%) received SRS followed by EGFR-TKI. The median follow-up was 22 months (interquartile range, 13-35). Patient characteristics are listed in Table 1. The median age at brain metastasis diagnosis for the EGFR-TKI, WBRT, and SRS groups was 60, 58, and 63 years, respectively. Patients who received upfront EGFR-TKI were less likely to have symptomatic brain metastases (12% EGFR-TKI *v* 51% WBRT and 49% SRS; $P < .001$) and were more likely to have brain metastases ≤ 1 cm (66% EGFR-TKI *v* 35% WBRT and 44% SRS; $P < .001$). Patients who received upfront WBRT were more likely to have a less favorable prognosis (ds-GPA of 0-1.5; 75% WBRT *v* 59% EGFR-TKI and 52% SRS; $P = .001$) and have > 10 brain metastases (37% WBRT *v* 15% EGFR-TKI and 7% SRS; $P < .001$). Patients treated with upfront EGFR-TKI and upfront WBRT were more likely to be stage IV at diagnosis (91% EGFR-TKI and 92% WBRT *v* 80% SRS; $P = 0.014$). There was no difference between the three groups with respect to age, sex, ECOG performance status, smoking status, EGFR mutation, and extracranial metastases at the time of brain metastases.

Survival Outcomes

For the entire cohort, the median OS after brain metastases was 30 months (95% CI, 27 to 34). The median OS for the upfront

Table 1. Patient Characteristics

Characteristic	EGFR-TKI (n = 131) No.	EGFR-TKI (n = 131) %	WBRT (n = 120) No.	WBRT (n = 120) %	SRS (n = 100) No.	SRS (n = 100) %	*P*
Age at brain metastases, years							
Median	60		58		63		.15
Interquartile range	53-70		51-65		54-70		
< 50	22	17	24	20	18	18	.103
50- < 60	37	28	43	36	19	19	
60- < 70	38	29	33	27	36	36	
≥ 70	34	26	20	17	27	27	
Sex							
Female	91	69	77	64	68	68	.66
Male	40	31	43	36	32	32	
Stage at diagnosis							
I-III	12	9	10	8	20	20	.014
IV	119	91	110	92	80	80	
ECOG performance status							
0-1	101	77	87	73	68	68	.302
2-3	30	23	33	27	32	32	
Disease-specific graded prognostic assessment							
0-1.5	78	60	90	75	52	52	.001
2.0-3.5	53	40	30	25	48	48	
Smoking status							
Current/former	89	68	76	63	62	62	.543
Never	42	32	44	37	38	38	
Symptomatic brain metastases							
No	115	88	69	49	51	51	< .001
Yes	16	12	61	51	49	49	
No. of brain metastases							
1	30	23	7	6	32	32	< .001
2-4	54	41	25	21	50	50	
5-10	27	21	44	37	11	11	
> 10	20	15	44	37	7	7	
Size of largest brain metastasis							
≤ 1 cm	87	66	42	35	44	44	< .001
> 1 cm	44	34	78	65	56	56	
EGFR mutation							
Exon 19	82	62	80	67	59	59	.619
Exon 20	5	4	6	5	7	7	
Exon 21	44	34	34	28	34	34	
Extracranial metastases at time of brain metastases							
Yes	29	22	26	22	28	28	.478
No	102	78	94	78	72	72	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR epidermal growth factor receptor; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

SRS, WBRT, and EGFR-TKI groups was 46 months (95% CI, 37 to 57), 30 months (95% CI, 27 to 38), and 25 months (95% CI, 20 to 28), respectively (log-rank $P < .001$; Fig 1). OS at 2 years for the upfront SRS, WBRT, and EGFR-TKI groups was 78% (95% CI, 66% to 85%), 62% (95% CI, 52% to 70%), and 51%, (95% CI, 42% to 60%), respectively. After controlling for significant covariables in a multivariable model including age, ECOG performance status, number of brain metastases, EGFR mutation, and extracranial metastases, upfront SRS was independently associated with improved OS relative to EGFR-TKI (adjusted hazard ratio, 0.39; 95% CI, 0.26 to 0.58; $P < .001$; Table 2). Upfront WBRT was also associated with improved OS relative to EGFR-TKI (adjusted hazard ratio, 0.70; 95% CI 50% to 98%; $P = .039$). There was no difference in survival when analyzed by individual institution, $P = .43$. These results were unchanged after propensity score matching (Appendix; Appendix Tables A1, A2, and A3; Fig A1, online only).

Intracranial Progression

In the context of the competing risk of death, using the method of Fine and Gray, the median time to intracranial progression for the upfront SRS, WBRT, and EGFR-TKI groups was 23 months (95% CI, 18 to 28), 24 months (95% CI, 21 to 30), and 17 months (95% CI, 14 to30), respectively (log-rank $P = .025$).[15] Using a competing risks regression model, upfront SRS and WBRT were associated with trends toward lower probability of intracranial progression after controlling for EGFR mutation status, with adjusted subdistribution hazard ratios of 0.73 (95% CI, 0.52 to 1.02; $P = .062$) and 0.92 (95% CI, 0.66 to 1.29; $P = .640$), respectively (Table 3; Fig 2).

Additional Subgroup Analyses

To identify potential differences in the benefits of upfront SRS in patients by varying prognosis, we subdivided patients by ds-GPA: upfront SRS GPA, 0 to 1.5 (n = 52; 15%); upfront WBRT GPA, 0 to

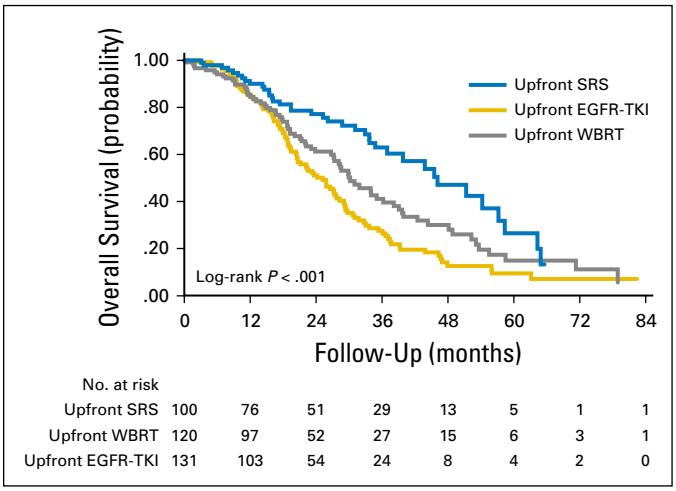


Fig 1. Kaplan-Meier analysis comparing overall survival in patients treated with upfront stereotactic radiosurgery (SRS), upfront whole-brain radiotherapy (WBRT), and upfront epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI).

1.5 (n = 90; 26%); upfront EGFR-TKI GPA, 0 to 1.5 (n = 78; 22%); upfront SRS GPA 2 to 4 (n = 48; 14%); upfront WBRT GPA 2 to 4 (n = 30; 8%); and upfront EGFR-TKI GPA, 2 to 4 (n = 53; 15%). Patients with a more favorable prognosis (dsGPA, 2-4) who received upfront SRS had a longer median OS (64 months; 95% CI, 46 to not reached) than those treated with WBRT (52 months; 95% CI, 32 to 79) or those who received EGFR-TKI followed by RT at intracranial progression (32 months; 95% CI, 26 to 39; Fig 3). Those with a less favorable prognosis (dsGPA, 0-1.5) also demonstrated improved outcomes when treated with upfront SRS (median, 33 months; 95% CI, 19 to 44; Fig 3) compared with those who received upfront WBRT (27 months; 95% CI, 19 to 30) and EGFR-TKI (19 months; 95% CI, 17 to 25).

Salvage Radiotherapy

Of the 131 patients who received upfront EGFR-TKI, 68 (52%) developed intracranial disease progression and were treated with RT (29 with SRS alone, 29 with WBRT alone, and 10 with SRS and WBRT). Of the 120 patients treated with upfront WBRT followed by EGFR-TKI, 29 (24%) required subsequent SRS (median, 1; range, 1-2). Of the 100 patients who received upfront SRS followed by EGFR-TKI, 25 (25%) underwent SRS at a later time (median, 1; range, 1-5), 11 (11%) subsequently underwent WBRT, and 8 (9%) eventually received both SRS and WBRT.

Subsequent Systemic Therapies

Of the 351 patients, 344 (98%) received erlotinib as first-line EGFR-TKI therapy. Progression of disease (extracranial or intracranial) was observed in 76% of the 351 patients, and patients subsequently received the following systemic therapies: carboplatin (or cisplatin) plus pemetrexed (45%), afatinib plus cetuximab (16%), clinical trial (15%), pemetrexed alone (10%), carboplatin (or cisplatin) plus paclitaxel (9%), and other (5%). On Cox proportional hazards analysis, subsequent systemic therapy use was not associated with OS (P = .82).

Table 2. Univariable and Multivariable Analyses of Covariables Associated With OS

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Upfront WBRT *v* upfront EGFR-TKI	0.72	0.53 to 0.98	.039	0.70	0.50 to 0.98	.039
Upfront SRS *v* upfront EGFR-TKI	0.45	0.31 to 0.66	< .001	0.39	0.26 to 0.58	< .001
Age at brain metastases, years						
50- < 60 *v* < 50	1.35	0.88 to 2.06	.18	1.51	0.98 to 2.34	.062
60- < 70 *v* < 50	1.47	0.97 to 2.50	.071	1.48	0.96 to 2.27	.074
> 70 *v* < 50	1.65	1.04 to 2.59	.032	1.69	1.06 to 2.69	.028
Sex						
Male *v* female	0.85	0.62 to 1.12	.236			
Stage at diagnosis						
IV *v* I-III	1.25	0.78 to 2.00	.346			
ECOG performance status						
2-3 *v* 0-1	2.12	1.57 to 2.87	< .001	2.45	1.78 to 3.67	< .001
Smoking status						
Never *v* current/former	1.23	0.93 to 1.64	.154			
Symptomatic brain metastases						
Yes *v* no	0.84	0.60 to 1.17	.305			
No. of brain metastases						
2-4 *v* 1	1.88	1.21 to 2.92	.005	1.52	0.96 to 2.40	.074
5-10 *v* 1	2.12	1.31 to 3.43	.002	1.34	0.80 to 2.25	.270
> 10 *v* 1	2.96	1.79 to 4.89	< .001	1.64	0.96 to 2.78	.067
Size of largest brain metastasis						
1 cm *v* ≤ 1 cm	0.97	0.73 to 1.30	.851			
EGFR mutation						
Exon 20 *v* exon 19	0.68	0.34 to 1.35	.266	0.62	0.31 to 1.25	.185
Exon 21 *v* exon 19	1.51	1.11 to 2.02	.008	1.75	1.29 to 2.38	< .001
Extracranial metastases at time of brain metastases						
No *v* yes	2.69	1.87 to 3.86	< .001	3.12	2.09 to 4.64	< .001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

Table 3. Univariable and Multivariable Analyses of Covariables Associated With Intracranial Progression-Free Survival (competing risks regression)

Variable	Univariable Analysis			Multivariable Analysis		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Upfront WBRT *v* upfront EGFR-TKI	0.72	0.52 to 1.00	.048	0.73	0.53 to 1.02	.062
Upfront SRS *v* upfront EGFR-TKI	0.89	0.63 to 1.26	.516	0.92	0.66 to 1.29	.640
Age at brain metastases, years						
50 to < 60 *v* 50	1.29	0.87 to 1.91	.205			
60 to < 70 *v* 50	1.05	0.70 to 1.57	.798			
> 70 *v* 50	1.07	0.70 to 1.68	.731			
Sex						
Male *v* female	0.84	0.63 to 1.13	.250			
Stage at diagnosis						
IV *v* I-III	0.76	0.44 to 1.23	.260			
ECOG performance status						
2-3 *v* 0-1	0.98	0.70 to 1.36	.885			
Smoking status						
Never *v* current/former	0.90	0.68 to 1.21	.495			
Symptomatic brain metastases						
Yes *v* no	1.26	0.93 to 1.71	.129			
No. of brain metastases						
2-4 *v* 1	1.06	0.72 to 1.56	.779			
5-10 *v* 1	0.79	0.50 to 1.25	.322			
> 10 *v* 1	1.15	0.73 to 1.83	.548			
Size of largest brain metastasis						
1 cm *v* ≤ 1 cm	1.00	0.76 to 1.34	.974			
EGFR mutation						
Exon 20 *v* exon 19	1.29	0.78 to 2.15	.312	1.30	0.78 to 2.15	0.312
Exon 21 *v* exon 19	1.51	1.10 to 2.04	.009	1.51	1.11 to 2.05	0.009
Extracranial metastases at time of brain metastases						
No *v* yes	1.18	0.85 to 1.63	.317			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; SHR, subdistribution hazard ratio; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

DISCUSSION

To our knowledge, this is the largest pooled analysis in the literature of patients with EGFR-mutant NSCLC who developed brain metastases before initiating therapy with erlotinib (EGFR-TKI administered to 98% of patients). For this cohort of patients, the use of SRS followed by EGFR-TKI was associated with the longest OS. The median OS for the patients treated with SRS followed by EGFR-TKI, WBRT followed by EGFR-TKI, and EGFR-TKI followed by SRS or WBRT at intracranial progression was 47, 31, and 25 months, respectively. The OS of 25 months in the erlotinib group compares favorably with prior studies evaluating the use of upfront EGFR-TKI (median OS, 15.9-20.9 months).[11,12,16]

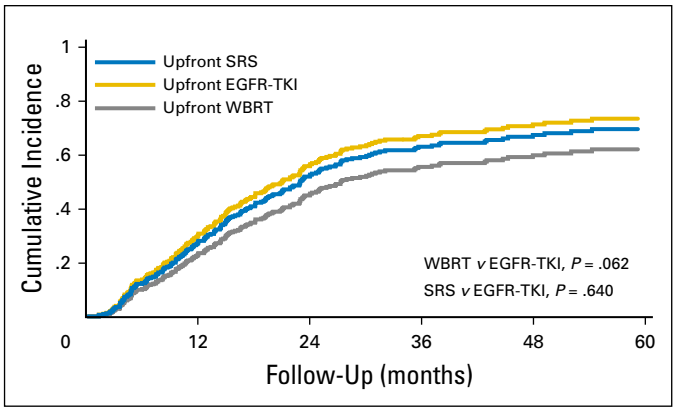
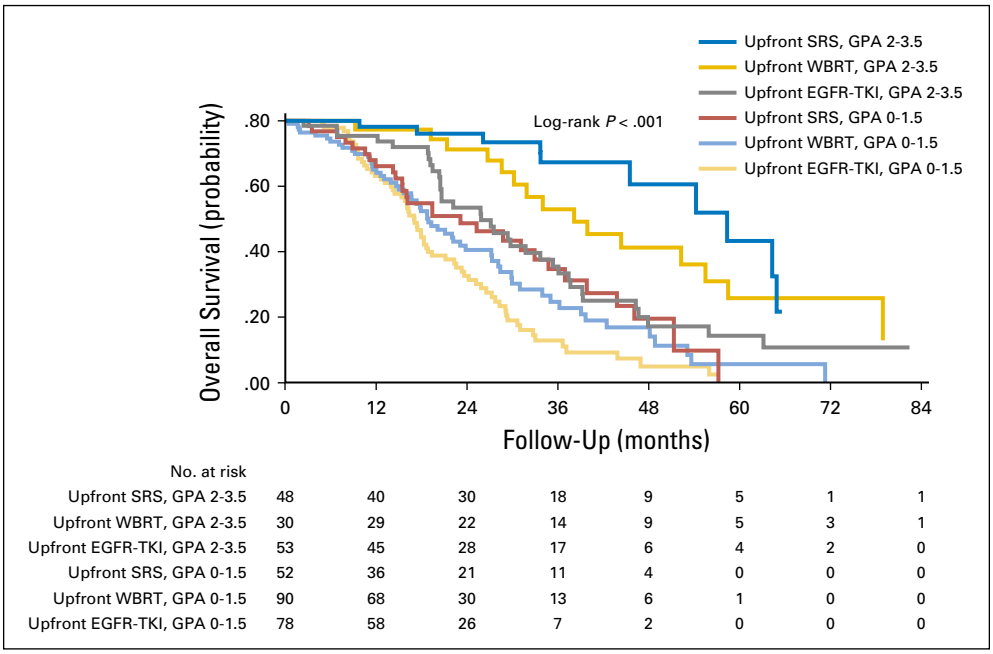


Fig 2. Cumulative incidence of intracranial progression using competing risks regression analysis in patients treated with upfront stereotactic radiosurgery (SRS), upfront whole-brain radiotherapy (WBRT), and upfront epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI).

In addition to demonstrating the longest OS after the development of brain metastases, patients treated with upfront SRS were more likely to have brain metastases > 1 cm and were more likely to be symptomatic from their brain metastases compared with patients treated with upfront EGFR-TKI. Most important, validated prognostic indices, such as ds-GPA, performance status, age, number of brain metastases, presence of extracranial metastases, and *EGFR* mutation exon location, were similar between the SRS followed by EGFR-TKI and EGFR-TKI groups. The current findings suggest that the improved OS seen in the upfront SRS group is not secondary to selection bias or differences between patient cohorts, but due to treatment of CNS disease. Similarly, a systematic review and meta-analysis of 12 studies found that cranial RT (SRS or WBRT) followed by erlotinib improved OS and intracranial PFS compared with upfront erlotinib in patients with EGFR-mutant NSCLC who developed brain metastases.[17]

The impact of upfront RT on patient outcomes was most pronounced in patients with a more favorable prognosis (dsGPA, 2-4). Patients with more favorable prognostic features who received SRS followed by erlotinib had a median OS of 64 months, compared with only 32 months in patients treated initially with erlotinib ($P < .001$). In addition, a multivariable analysis of patient



No. at risk								
Upfront SRS, GPA 2-3.5	48	40	30	18	9	5	1	1
Upfront WBRT, GPA 2-3.5	30	29	22	14	9	5	3	1
Upfront EGFR-TKI, GPA 2-3.5	53	45	28	17	6	4	2	0
Upfront SRS, GPA 0-1.5	52	36	21	11	4	0	0	0
Upfront WBRT, GPA 0-1.5	90	68	30	13	6	1	0	0
Upfront EGFR-TKI, GPA 0-1.5	78	58	26	7	2	0	0	0

Fig 3. Kaplan-Meier analysis comparing overall survival in patients treated with upfront stereotactic radiosurgery (SRS), upfront whole-brain radiotherapy (WBRT), and upfront epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), stratified by disease specific Graded Prognostic Assessment (GPA).

characteristics demonstrated that SRS versus EGFR-TKI, WBRT versus EGFR-TKI, performance status, age, *EGFR* exon 19 mutation, and absence of extracranial metastases were associated with improved OS. Patients with more than 10 brain metastases showed the strongest trend toward decreased OS, although it did not reach statistical significance ($P = .067$).

The oligometastatic state initially postulated by Weischselbaum has led to an abundance of studies demonstrating that treatment of metastatic sites with radiotherapy or surgical resection can improve survival in patients with limited metastases.[18-20] Before the development of targeted therapies, a meta-analysis of 757 patients with oligometastatic NSCLC treated with ablative therapy to all sites of disease demonstrated a median 5-year OS of 29%, far greater than a historical control of 2%.[19,21] As in our study, the authors found that limited extracranial disease burden was associated with prolonged OS. In the current era of targeted therapy, a series evaluating the use of local ablative therapies after the development of EGFR resistance mutation reported a median OS of 41 months from the time of treatment, suggesting a potential benefit of local therapy.[22]

The improvement in OS observed in patients who received upfront SRS in our study may be explained by this same oligometastatic phenomenon. The high biologically effective doses of radiotherapy inherent in SRS may ablate intracranial metastases, whereas erlotinib simultaneously controls extracranial disease (and potentially intracranial micrometastatic disease), resulting in prolonged survival. Multiple studies have shown EGFR-mutant NSCLC to be highly radiosensitive in both the preclinical and clinical settings, thereby making the ablation of brain metastases a distinct possibility.[23,24] Two large series evaluating the efficacy of SRS in the treatment of EGFR-mutant brain metastases reported local control rates of 100% and 93%.[23,25]

In addition to the potential for SRS to improve OS compared with WBRT, numerous studies have demonstrated that SRS has less acute and late toxicity.[26-28] Given the prolonged survival of patients with EGFR-mutant NSCLC, the use of SRS to defer (or completely avoid) the neurocognitive sequelae of WBRT is of particular importance. In a large, multicenter prospective trial that randomly assigned patients to WBRT, observation after surgical resection, or SRS, patients who received WBRT reported worse health-related quality-of-life scores, but no improvement in OS.[27] Patients in the observation arm reported less fatigue, better global health status, and improved cognitive functioning at various time points.[27] In addition, a recently published prospective study investigating the impact of SRS on neurocognitive function and health-related quality of life found that SRS did not negatively affect either domain.[28] Furthermore, a timely delivery of a single fraction of SRS allows for the prompt initiation of systemic therapy, compared with the 2- to 3-week delay that may be required when WBRT is administered.

Historically, patients with multiple brain metastases were treated with WBRT, whereas SRS was reserved for patients with fewer brain metastases or more favorable prognostic features. However, a prospective study of over 1,000 patients treated with SRS alone found that the OS for patients with five to 10 brain metastases was noninferior to that for patients with two to four brain metastases.[29] Furthermore, the National Comprehensive Cancer Network guidelines state that SRS alone may be a suitable treatment option for patients with four or more brain metastases with a good performance status and low overall tumor volume.[30]

Although the results of this multi-institutional study are potentially practice changing, there are limitations to the study. First, although we attempted to recreate a prospective study by the exclusionary criteria set forth, the study is retrospective and carries with it all of the biases inherent in such an analysis. Specifically, excluding patients with missing covariables could lead to selection bias, although we have no reason to believe that groups of patients were more or less likely to be excluded based on insufficient information in the medical record. Second, patients were treated at large, academic centers that have access to investigational systemic

agents that may not be available at smaller academic centers or in the community. Third, although the ds-GPA was similar between groups, the method by which patients were selected to receive EGFR-TKI, SRS, or WBRT as their first therapy was not random and may have contributed to study bias. Fourth, we did not account for the potential toxicities associated with local therapies and their impact on quality of life. Finally, in our single-institution analysis,[9] in which we were able to parse out local and distant intracranial control, the local control benefit of SRS was clearly evident. Unfortunately, in a multi-institutional study of this nature, it would not have been feasible to ask every center to perform such an analysis.

In conclusion, the present multi-institutional analysis demonstrates that the use of upfront EGFR-TKI, and deferral of radiotherapy, is associated with inferior OS in patients with EGFR-mutant NSCLC who develop brain metastases. SRS followed by EGFR-TKI was associated with the longest OS and allowed patients to avoid the potential neurocognitive sequelae of WBRT. A prospective, multi-institutional randomized trial of SRS followed by EGFR-TKI versus EGFR-TKI followed by SRS at intracranial progression is urgently needed. Until such a study is conducted and published, the standard-of-care treatment of newly diagnosed brain metastases should remain SRS followed by systemic therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Brain Metastases in Tyrosine Kinase Inhibitor–Naïve Epidermal Growth Factor Receptor–Mutant Non–Small-Cell Lung Cancer: A Retrospective Multi-Institutional Analysis

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Appendix

Propensity Score-Matched Analysis

Propensity score matching was used to address potential treatment selection bias. Groups were matched on the basis of propensity scores associated with treatment selection using logistic regression and one-to-one nearest-neighbor matching without replacement. Covariable balance after matching across the treatment and control groups were assessed using standardized differences of means.

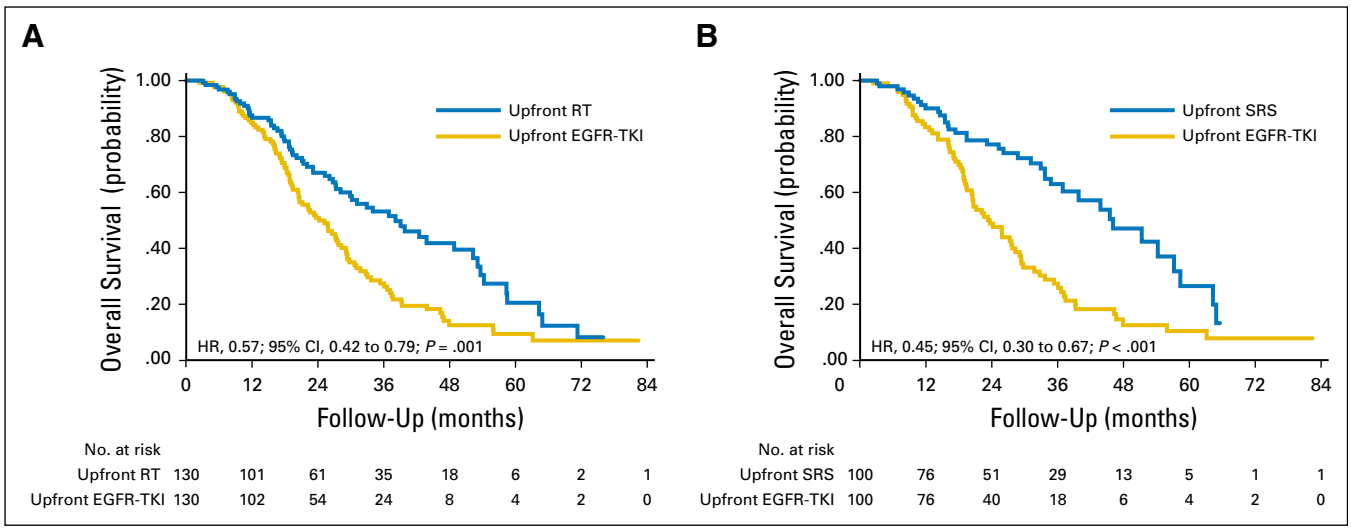

Fig A1. Kaplan-Meier overall survival stratified by treatment regimen for propensity score–matched cohorts. (A) Match 1: 131 patients receiving EGFR-TKI to 131 patients receiving RT (RT = SRS + WBRT). Median survival: EGFR-TKI, 24 months, 95% CI, 20 to 28 months; RT, 38 months, 95% CI, 28 to 52 months. (B) Match 2: 100 EGFR-TKI patients to 100 SRS patients. Median survival: EGFR-TKI, 23 months, 95% CI, 19 to 28 months; SRS, 46 months, 95% CI, 37 to 57 months. EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; RT, radiotherapy; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

Table A1. Match 1: 131 Patients Receiving EGFR-TKI to 131 Patients Receiving RT (RT = SRS + WBRT)

	Propensity Score–Matched Covariables			
	Unmatched		Matched	
Characteristic	Absolute Standardized % Bias	*P*	Absolute Standardized % Bias	*P*
Stage at diagnosis	89.2	< .001	9.1	.337
Symptomatic brain metastases	25.1	.024	11.1	.275
No. of brain metastases	56.7	< .001	12.2	.347
Size of largest brain metastasis	20.4	< .001	−1.3	.581
Institution	12.2	< .001	2.7	.467

Abbreviations: EGFR, epidermal growth factor receptor; RT, radiotherapy; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy.

Table A2. Match 2: 100 EGFR-TKI Patients to 100 SRS Patients

Propensity Score-Matched Covariables				
	Unmatched		Matched	
Characteristic	Absolute Standardized % Bias	*P*	Absolute Standardized % Bias	*P*
Stage at diagnosis	−18.6	< .001	−2.5	.348
Symptomatic brain metastases	−17.5	< .001	−0.5	.847
No. of brain metastases	−7.9	< .001	0.7	.774
Size of largest brain metastasis	−11.7	< .001	0.9	.699
Institution	−18.6	< .001	−2.5	.348

Abbreviations: EGFR, epidermal growth factor receptor; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitors.

Table A3. No. of Patients by Institution

Institution	No. of Patients
Memorial Sloan Kettering Cancer Center	162
University of Colorado	61
Yale	50
University of California San Francisco	37
Cleveland Clinic	25
Vanderbilt	16