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Article

Comparison of first-line radiosurgery for small-cell and non-small cell lung cancer brain metastases (CROSS-FIRE)

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Abstract

Introduction: Historical reservations regarding stereotactic radiosurgery (SRS) for small-cell lung cancer (SCLC) brain metastases include concerns for short-interval and diffuse central nervous system (CNS) progression, poor prognoses, and increased neurological mortality specific to SCLC histology. We compared SRS outcomes for SCLC and non-small cell lung cancer (NSCLC) where SRS is well established.

Methods: Multicenter first-line SRS outcomes for SCLC and NSCLC from 2000 to 2022 were retrospectively collected (n = 892 SCLC, n = 4785 NSCLC). Data from the prospective Japanese Leksell Gamma Knife Society (JLGK0901) clinical trial of first-line SRS were analyzed as a comparison cohort (n = 98 SCLC, n = 814 NSCLC). Overall survival (OS) and CNS progression were analyzed using Cox proportional hazard and Fine-Gray models, respectively, with multivariable adjustment for cofactors including age, sex, performance status, year, extracranial disease status, and brain metastasis number and volume. Mutation-stratified analyses were performed in propensity score–matched retrospective cohorts of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) positive NSCLC, mutation-negative NSCLC, and SCLC.

Results: OS was superior for patients with NSCLC compared to SCLC in the retrospective dataset (median OS = 10.5 vs 8.6 months; $P < .001$) and in the JLGK0901 dataset. Hazard estimates for first CNS progression favoring NSCLC were similar in both datasets but reached statistical significance in the retrospective dataset only (multivariable hazard ratio = 0.82, 95% confidence interval = 0.73 to 0.92, $P = .001$). In the propensity score–matched cohorts, there were continued OS advantages for NSCLC patients (median OS = 23.7 [EGFR and ALK positive NSCLC] vs 13.6 [mutation-negative NSCLC] vs 10.4 months [SCLC], pairwise P values < 0.001), but no statistically significant differences in CNS progression were observed in the matched cohorts. Neurological mortality and number of lesions at CNS progression were similar for NSCLC and SCLC patients. Leptomeningeal progression was increased in patients with NSCLC compared to SCLC in the retrospective dataset only (multivariable hazard ratio = 1.61, 95% confidence interval = 1.14 to 2.26, $P = .007$).

Conclusions: After SRS, SCLC histology was associated with shorter OS compared to NSCLC. CNS progression occurred earlier in SCLC patients overall but was similar in patients matched on baseline factors. SCLC was not associated with increased neurological mortality, number of lesions at CNS progression, or leptomeningeal progression compared to NSCLC. These findings may better inform clinical expectations and individualized decision making regarding SRS for SCLC patients.

International guideline statements recommend stereotactic radiosurgery (SRS) for limited brain metastases (BrM) arising from most tumor histologies (1-4) due to the results of randomized trials that demonstrate similar overall survival (OS) and improved cognition and quality of life with SRS alone vs strategies incorporating whole-brain radiotherapy (WBRT) (5-9). Small-cell lung cancer (SCLC) patients, however, were systematically excluded from the landmark trials establishing SRS alone, and WBRT has remained the standard of care for SCLC BrM (10,11).

Our group previously published a large international retrospective analysis, the First-line Radiosurgery for Small-Cell Lung Cancer (FIRE-SCLC) study, comparing SRS vs WBRT that demonstrated superior intracranial disease control with WBRT without a resulting improvement in OS (12). Those observations suggested that the trade-offs associated with SRS in SCLC BrM may be similar to other tumor histologies where SRS is well established and supported the development of an ongoing cooperative group phase III randomized trial of SRS vs hippocampal-avoidant WBRT for SCLC BrM (NCT04804644).

Modern trends in SCLC management including decreases in prophylactic cranial irradiation, increases in central nervous system (CNS) surveillance with high-resolution magnetic resonance imaging (MRI), and longer OS with the addition of immunotherapy are expected to lead to the identification of more SCLC patients with limited BrM who are potential candidates for SRS (10,11,13-17). However, due to the historical paucity of data on first-line SRS in SCLC, concerns remain regarding the potential for short-interval and diffuse CNS progression, poor prognoses, and increased neurological mortality specific to SCLC histology (18-20). Most of the data regarding the CNS predilection of SCLC relative to other tumor histologies have characterized the incidence of BrM from diagnosis through the natural disease course (21-26), whereas very limited comparative data are available on post-SRS outcomes in patients who have already developed BrM (27). The purpose of this analysis was to provide a detailed comparison of SRS outcomes in SCLC relative to the established benchmark of SRS in non-small cell lung cancer (NSCLC), which represents the most common cause of BrM and the most frequent tumor histology for patients treated in the landmark clinical trials establishing SRS alone (6,9,28).

Methods

The Comparison of First-line Radiosurgery for SCLC and NSCLC Brain Metastases (CROSS-FIRE) study included patients treated with first-line SRS without prior WBRT or prophylactic cranial irradiation. Two separate analytic cohorts were included: a retrospective dataset and a comparison prospective dataset from the published Japanese Leksell Gamma Knife Society (JLGK0901) trial (29).

Details regarding the data collection for the retrospective SCLC cohort were previously described (12), with new centers, updated follow-up, and additional endpoints included for this analysis. SCLC data were collected from 30 centers in Japan, the United States, Canada, France, Taiwan, Switzerland, and Germany, and a comparison NSCLC cohort was collected from 7 centers in Japan, Germany, and the United States (Supplementary Table 1, available online). Participation was supported by the International Radiosurgery Research Foundation (IRR-F.org). Participating centers obtained local institutional review board approval with informed consent exemptions due to the minimal risk of harm. Included patients had tissue-confirmed SCLC or NSCLC and received first-line single-fraction or multi-fraction SRS for BrM from years 2000 to 2022. SRS was defined per a consensus definition modified to allow up to 6 SRS fractions (30).

JLGK0901 was a single-arm prospective study of first-line single-fraction SRS for 1-10 BrM from mixed tumor histologies. Inclusion criteria, consent procedures, SRS details, follow-up protocols, and endpoints were previously described (29). Among the 1194 patients enrolled at 23 centers in Japan, 912 (76%) had BrM from lung cancer and were included in this analysis.

Statistical analysis

The primary endpoints of interest were OS, first CNS progression (FCP), distant CNS progression (DCP) (ie, new brain lesions), and local CNS progression (LCP) in SRS-treated lesions. LCP and DCP were independently tracked, with local control followed beyond isolated distant progression without censoring and vice versa. Secondary endpoints evaluated in patients with available data included neurological mortality, leptomeningeal disease (LMD) progression, number of lesions at FCP, rates of salvage therapy, and treatment-related adverse effects. Detailed time-to-event outcome definitions and censoring procedures are displayed in Supplementary Table 2 (available online). Neurological mortality included cases of likely or possible death due to BrM in the retrospective dataset, and in JLGK0901 this was assigned by the treating investigator with uncertain causes of death counted in the neurological mortality group.

Time-to-event outcomes were measured from SRS delivery. Median follow-up was calculated using the reverse Kaplan-Meier method (31). The OS hazard ratio (HR) and 95% confidence interval (CI) comparing SCLC and NSCLC were estimated with Cox proportional hazard regression. Kaplan-Meier curves were used to estimate medians. For the other time-to-event outcomes, the hazard ratio and 95% confidence interval were analyzed with Fine-Gray models to account for the competing risk of death. The cumulative incidence function was used to estimate the 12-month and 24-month incidence rates. Multivariable models in the retrospective dataset were adjusted for region (Asia vs North America and Europe), year, sex, Karnofsky Performance Status, extracranial metastases outside the thoracic tumor and regional lymph nodes, presence of BrM at diagnosis (synchronous vs metachronous), BrM number, and total BrM volume. Models were adjusted on similar factors in the JLGK0901 dataset with the exceptions of inapplicable region, unavailable data on year and presence of BrM at diagnosis, and extracranial disease control was used rather than unavailable data on the presence of extracranial metastases. The hazard ratio and 95% confidence interval for all time-to-event outcomes were modeled with multivariable adjustment for the factors above except for the propensity score-matched analyses described below, where the matching procedures controlled for baseline variables. Cumulative treatment-related adverse events were compared with Fisher's exact test because low event rates precluded multivariable modeling. Salvage therapy rates were analyzed with multivariable logistic regression models.

The first stage of the analysis compared SCLC patients with all NSCLC patients for the outcomes above in the retrospective and JLGK0901 datasets. Then subset analyses were performed with propensity score matching (PSM) that compared SCLC patients with NSCLC patients in the retrospective cohort that were further stratified into those with epidermal growth factor receptor (EGFR) mutated or anaplastic lymphoma kinase (ALK) gene-rearranged NSCLC vs mutation-negative NSCLC. All molecularly stratified analyses were limited to years 2005 and after following the landmark publications establishing the sensitivity of EGFR mutated NSCLC to tyrosine kinase inhibitors (TKIs) targeting EGFR (32-34). Direct molecular data were unavailable in JLGK0901, but data regarding EGFR-directed TKIs (gefitinib and erlotinib) delivered during or after SRS were prospectively collected. Stratified PSM analyses were performed in the JLGK0901 dataset using TKI receipt as a surrogate for EGFR status in NSCLC patients (EGFR TKI positive vs negative). For the mutation and TKI-stratified analyses, 3-way (1:1:1) PSM was performed to create cohorts balanced for the same baseline factors as the multivariable models described above using the methods described by Rassen et al (35). The matched groups were compared for OS and the primary CNS control outcomes (Supplementary Methods, available online).

All hypothesis tests were 2-sided, and P less than .05 was considered statistically significant. All analyses were performed in R version 4.1.2 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute) by the University of Colorado Cancer Center Biostatistics Core.

Results

The retrospective dataset included 892 SCLC and 4785 NSCLC patients treated with SRS from years 2000 to 2022. JLGK0901 included 98 SCLC and 814 NSCLC patients treated with SRS from 2009 to 2012. Compared with NSCLC, patients with SCLC had a higher total BrM volume, had older age, were more frequently male, had higher rates of controlled extracranial disease, and had treatment in later years (Table 1). Most patients were treated in Asia, predominately Japan, and the percentage treated in Asia was higher in the retrospective NSCLC cohort compared to the SCLC cohort. Most of the patients in the retrospective dataset (95.7%) were treated with single-fraction SRS, and the radiation doses delivered were similar, although slightly higher for NSCLC. The median follow-up was 61.9 months and 49 months in the retrospective and JLGK0901 datasets, respectively.

SCLC vs NSCLC: OS and CNS progression

In the retrospective dataset, OS was superior for patients with NSCLC over SCLC (median OS, 10.5 vs 8.6 months; multivariable HR = 0.79, 95% CI = 0.73 to 0.86, $P < .001$). Multivariable Fine-Gray models for CNS progression demonstrated a statistically significant reduction in the hazard of FCP for NSCLC vs SCLC (multivariable HR = 0.82, 95% CI = 0.73 to 0.92, $P = .001$) and DCP (multivariable HR = 0.82, 95% CI = 0.73 to 0.93, $P = .002$). No statistically significant differences were observed in LCP on multivariable analysis (Figure 1; Table 2).

In JLGK0901, OS was superior for NSCLC over SCLC (median OS = 13.0 vs 8.7 months; multivariable HR = 0.68, 95% CI = 0.54 to 0.85, $P = .001$). Multivariable analyses of CNS progression in JLGK0901 returned similar hazard ratio estimates for FCP, DCP, and LCP for NSCLC vs SCLC compared with the retrospective dataset, but none of these comparisons reached statistical significance in the JLGK0901 dataset (Figure 1; Table 2).

SCLC vs NSCLC stratified by mutation and TKI status

In the retrospective dataset, 3-way PSM was performed to create SCLC, EGFR or ALK-positive NSCLC, and mutation-negative NSCLC cohorts balanced for baseline factors with 428 patients per group (1284 total; Supplementary Table 3, available online). Compared with SCLC, OS was superior for both mutation-negative NSCLC and mutation-positive NSCLC (median OS = 10.4 vs 13.6 vs 23.7 months, respectively; Figure 2). CNS progression models demonstrated no statistically significant differences between SCLC and either mutation-negative or mutation-positive NSCLC for FCP, DCP, or LCP (Figure 2; Supplementary Table 4, available online).

In JLGK0901, 3-way matching created balanced SCLC, EGFR TKI-positive NSCLC, and TKI-negative NSCLC cohorts with 84 patients per group (252 total; Supplementary Table 5, available online). Compared with SCLC, no differences in OS were observed with TKI-negative NSCLC, whereas OS was statistically significantly improved with EGFR TKI-positive NSCLC (median OS = 8.8

Table 1. Patient characteristics

		Retrospective				JLGK0901		
Variable	**Level**	**NSCLC (n = 4785)**	**SCLC (n = 892)**	**P**	**Level**	**NSCLC (n = 814)**	**SCLC (n = 98)**	**P**
Age, y	Median (IQR)	67 (60, 74)	68 (62, 74)	<.001[a]	Median (IQR)	67 (60, 74)	70 (62, 75)	.09[a]
Sex	Female	1734 (36.2%)	239 (26.8%)	<.001[b]	Female	280 (34.4%)	15 (15.3%)	<.001[b]
	Male	3051 (63.8%)	653 (73.2%)		Male	534 (65.6%)	83 (84.7%)	
Year	Median (IQR)	2010 (2005, 2015)	2013 (2006, 2017)	<.001[c]	Years	2009-2012	2009-2012	NA
Region	Asia	4230 (88.4%)	639 (71.6%)	<.001[b]	Asia	814 (100%)	98 (100%)	NA
	N. Am, Europe	555 (11.6%)	253 (28.4%)					
KPS	≥90	2828 (59.1%)	505 (56.6%)	.08[d]	≥90	599 (73.6%)	77 (78.6%)	.42[d]
	70-80	1532 (32.0%)	318 (35.7%)		70-80	192 (23.6%)	20 (20.4%)	
	≤60	425 (8.9%)	69 (7.7%)		≤60	23 (2.8%)	1 (1.0%)	
Extracranial status	ECM Absent	2446 (51.1%)	487 (54.6%)	.06[b]	Controlled	540 (66.3%)	76 (77.6%)	.03[b]
	ECM Present	2339 (48.9%)	405 (45.4%)		Uncontrolled	274 (33.7%)	22 (22.4%)	
BrM at diagnosis	No	3026 (63.2%)	591 (66.3%)	.09[b]		—	—	NA[e]
	Yes	1759 (36.8%)	301 (33.7%)			—	—	
BrM, No.	Median (IQR)	3 (1, 7)	3 (1, 6)	.41[c]	Median (IQR)	2 (1, 4)	2 (1, 4)	.70[c]
Total BrM volume (cc)	Median (IQR)	2.9 (0.8, 8.3)	4.5 (1.2, 11.9)	<.001[c]	Median (IQR)	1.4 (0.5, 3.5)	2.3 (0.7, 4.9)	.004[c]
SRS fractions	Median (IQR)	1 (1, 1)	1 (1, 1)	<.001[c]	Fractions	1 (all)	1 (all)	NA
	1 Fraction	4611 (96.4%)	822 (92.2%)					
	≥2 Fractions	174 (3.6%)	70 (7.8%)					
SRS dose	Median (IQR)	21 (20, 23)	20 (20, 22)	<.001[c]	Median (IQR)	22 (22, 22)	22 (20, 22)	.002[c]
	Mean (SD)	21 (3)	20 (3)		Mean (SD)	22 (1)	21 (1)	
Post-SRS brain MRI[f]	Yes	4088 (85.4%)	760 (85.2%)	.88[b]	Yes	735 (90.3%)	87 (88.8%)	.59[b]
	No	697 (14.6%)	132 (14.8%)		No	79 (9.7%)	11 (11.2%)	
Vital status, last FU	Alive/censor	770 (16.1%)	142 (15.9%)	NA	Alive/censor	112 (13.8%)	6 (6.1%)	NA
	Deceased	4015 (83.9%)	750 (84.1%)		Deceased	702 (86.2%)	92 (93.9%)	

[a] *P* values calculated via *t* test. BrM = brain metastases; ECM = extracranial metastases (outside of the thoracic tumor and regional lymph nodes); IQR = Interquartile range; JLGK = Japanese Leksell Gamma-Knife Society; KPS = Karnofsky performance status; NA = not applicable; N. Am = North America; NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer; SRS = stereotactic radiosurgery. FU = follow up.
[b] Fisher exact test.
[c] Nonparametric Kruskal-Wallis.
[d] Pearson χ^2.
[e] Data regarding the presence of BrM at diagnosis were unavailable in JLGK0901.
[f] Includes patients with at least 1 documented follow up brain MRI after completing first-line SRS.

vs 8.9 vs 27.8 months, respectively; Supplementary Figure 1, available online). CNS progression models returned no statistically significant differences in FCP, DCP, or LCP (Supplementary Figure 1; Supplementary Table 4, available online).

Neurological mortality and LMD progression

Analyses of neurological mortality and LMD progression were performed in all JLGK0901 patients and in retrospective patients with available data (neurological mortality: 831 SCLC, 4456 NSCLC; LMD: 468 SCLC, 1144 NSCLC). On multivariable analysis, no differences in neurological mortality were observed between SCLC and NSCLC in either the retrospective dataset (multivariable HR = 0.98, 95% CI = 0.80 to 1.20, *P* = .83) or JLGK0901 (multivariable HR = 1.35, 95% CI = 0.56 to 3.26, *P* = .50) (Figure 3; Supplementary Table 6, available online).

The risk of LMD was increased in patients with NSCLC compared to SCLC in the retrospective dataset (multivariable HR = 1.61, 95% CI = 1.14 to 2.26, *P* = .007), whereas no statistically significant differences were observed in JLGK0901 (Figure 3; Supplementary Table 6, available online). Mutation-based subset analyses in the retrospective dataset demonstrated an increased risk of LMD in patients with EGFR or ALK-positive NSCLC vs SCLC (multivariable HR = 2.19, 95% CI = 1.42 to 3.39, *P* < .001) but not in patients with mutation-negative NSCLC vs SCLC (multivariable HR = 1.10, 95% CI = 0.66 to 1.85, *P* = .71).

Number of lesions at first CNS progression

Data were available on the number of BrM at first CNS progression in 193 SCLC and 620 NSCLC patients in the retrospective dataset only. Full results for the comparison of SCLC vs NSCLC are presented in Supplementary Table 7 (available online). No statistically significant differences were observed in the number of BrM at CNS progression (SCLC vs NSCLC; median 2 vs 3; mean 5.6 vs 5.1, *P* = .83) or rates of progression with extensive (>10) BrM (16.6% [SCLC] vs 14.5% [NSCLC], *P* = .49). Analyses stratified by the number of BrM treated with first-line SRS (1, 2-4, 5-10, ≥11) also demonstrated no statistically significant differences. Similarly, analyses stratified by NSCLC mutation status also returned no statistically significant differences between SCLC and either EGFR or ALK-positive NSCLC or mutation-negative NSCLC (Figure 4).

Adverse events and salvage therapy

Among the 449 SCLC and 1131 NSCLC patients in the retrospective dataset with available data, the rates of treatment-related necrosis of any grade were 7.8% and 9.4%, respectively (*P* = .38). In JLGK0901, data were available in all patients for pooled rates of any Common Terminology for Adverse Events treatment-related toxicities, and the rates of any grade toxicity for SCLC and NSCLC were 5.1% and 9.6%, respectively (*P* = .19).

In the retrospective dataset, for SCLC and NSCLC the salvage SRS rates were 36.7% and 36.9%, respectively (*P* = .38), and the salvage WBRT rates were 15% and 7.3%, respectively (*P* < .001). In JLGK0901, for SCLC and NSCLC, the salvage SRS rates were 39.8% and 44.1%, respectively (*P* = .58), and the salvage WBRT rates were 20.4% and 10.9%, respectively (*P* < .001).

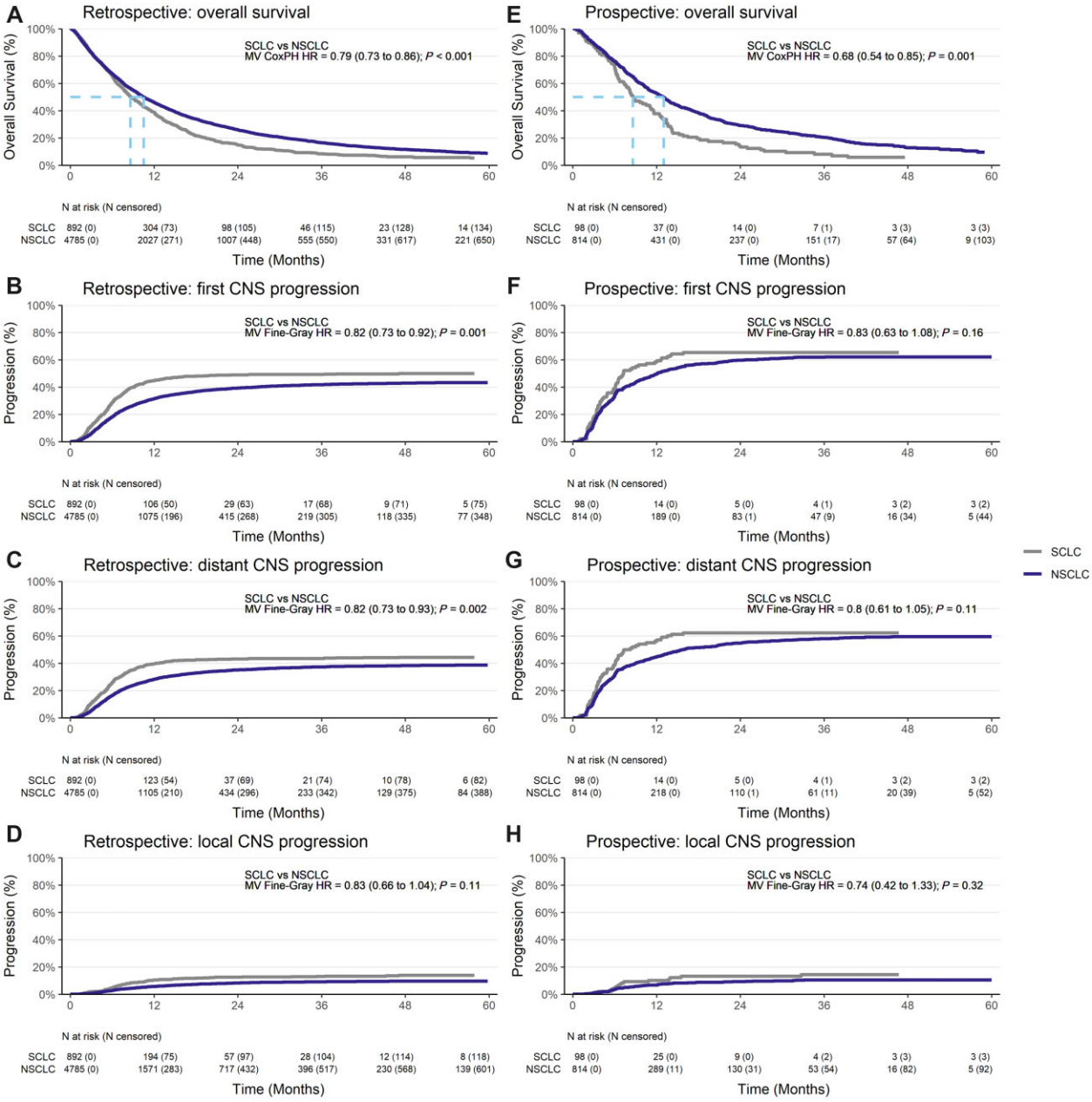

Figure 1. Overall survival (OS) and central nervous system (CNS) progression after first-line SRS for patients with small-cell lung cancer (SCLC) vs non-small cell lung cancer (NSCLC). **A**) Retrospective dataset, OS. **B**) Retrospective dataset, first CNS progression (FCP). **C**) Retrospective dataset, distant CNS progression (DCP). **D**) Retrospective dataset, local CNS progression (LCP). **E**) Japanese Leksell Gamma Knife Society (JLGK0901) (prospective dataset), OS. **F**) JLGK0901, FCP. **G**) JLGK0901, DCP. **H**) JLGK0901, LCP. The hazard ratio (HR) and 95% confidence interval (CI) for OS analyses were modeled using multivariable Cox proportional hazard regression (CoxPH). Hazard ratio and 95% confidence interval were modeled for CNS progression analyses using multivariable Fine-Gray models treating death as a competing risk. Multivariable models were adjusted for cofactors as described in the methods section.

Discussion

Survey data demonstrate that physicians are increasingly willing to consider first-line SRS in select SCLC patients (18), although concerns remain regarding the potential for short-interval and diffuse CNS progression, poor prognoses, and increased neurological mortality specific to SCLC histology. The CROSS-FIRE study, including over 6500 international patients, was designed to evaluate these considerations by comparing first-line SRS in SCLC with the established benchmark of SRS in NSCLC.

Median OS was 1.9 months longer for NSCLC over SCLC patients in the retrospective dataset and 4.3 months longer in JLGK0901. On PSM analyses stratified by NSCLC mutation status, median OS was superior for EGFR or ALK-positive NSCLC, followed by mutation-negative NSCLC, and then SCLC (23.7, 13.6, and 10.4 months, respectively). In analyses stratifying NSCLC patients by receipt of EGFR-directed TKIs as a surrogate for EGFR status in JLGK0901, OS was similar between TKI-negative NSCLC and SCLC, suggesting that the larger OS differences in JLGK0901 were driven primarily by the NSCLC patients who received EGFR-directed TKIs. The stratified survival outcomes observed after SRS demonstrating superior OS in EGFR or ALK-positive NSCLC and more similar OS for SCLC and mutation-negative NSCLC are consistent with existing prognostic data, such as the Graded-Prognostic-Assessment, for patients managed with various

Table 2. Overall survival (OS) and central nervous system (CNS) progression

Dataset	Outcomes	Group	Median, mo (95% CI)	12-mo % (95% CI)	24-mo % (95% CI)	Multivariable HR[a]	95% CI	P
Retrospective								
SCLC (N = 892)	OS	SCLC	8.6 (8.1 to 9.7)	—	—	Reference		
NSCLC (N = 4785)		NSCLC	10.5 (10.1 to 11.0)	—	—	0.79	0.73 to 0.86	<.001
	FCP	SCLC	—	44.8% (41.4 to 48.1)	48.8% (45.4 to 52.2)	Reference		
		NSCLC	—	31.5% (30.2 to 32.9)	39.3% (37.9 to 40.7)	0.82	0.73 to 0.92	.001
	DCP	SCLC	—	39.7% (36.4 to 43)	43.1% (39.7 to 46.4)	Reference		
		NSCLC	—	28.4% (27.1 to 29.7)	35.2% (33.8 to 36.6)	0.82	0.73 to 0.93	.002
	LCP	SCLC	—	10.5% (8.5 to 12.7)	12.5% (10.3 to 14.9)	Reference		
		NSCLC	—	5.8% (5.1 to 6.5)	8.3% (7.5 to 9.2)	0.83	0.66 to 1.04	.11
JLGK0901								
SCLC (N = 98)	OS	SCLC	8.7 (7.6 to 11.6)	—	—	Reference		
NSCLC (N = 814)		NSCLC	13.0 (11.7 to 13.9)	—	—	0.68	0.54 to 0.85	.001
	FCP	SCLC	—	59.2% (48.7 to 68.2)	65.3% (54.8 to 73.9)	Reference		
		NSCLC	—	49.8% (46.3 to 53.1)	59.6% (56.2 to 62.9)	0.83	0.63 to 1.08	.16
	DCP	SCLC	—	57.1% (46.6 to 66.3)	62.2% (51.7 to 71.1)	Reference		
		NSCLC	—	45.0% (41.5 to 48.3)	54.8% (51.3 to 58.2)	0.8	0.61 to 1.05	.11
	LCP	SCLC	—	10.2% (5.2 to 17.2)	13.3% (7.4 to 20.9)	Reference		
		NSCLC	—	6.8% (5.2 to 8.7)	9.2% (7.4 to 11.4)	0.74	0.42 to 1.33	.32

[a] Overall survival (OS), first CNS progression (FCP), distant CNS progression (DCP), local CNS progression in SRS-treated lesions (LCP). OS was evaluated with multivariable Cox proportional hazards regression, and CNS progression was modeled with multivariable Fine-Gray models. Multivariable models were adjusted for cofactors as described in the Methods section. The Kaplan-Meier method was used to calculate median OS, and the cumulative incidence function was used to estimate the 12-month and 24-month incidence rates for CNS progression outcomes as described in the Methods.

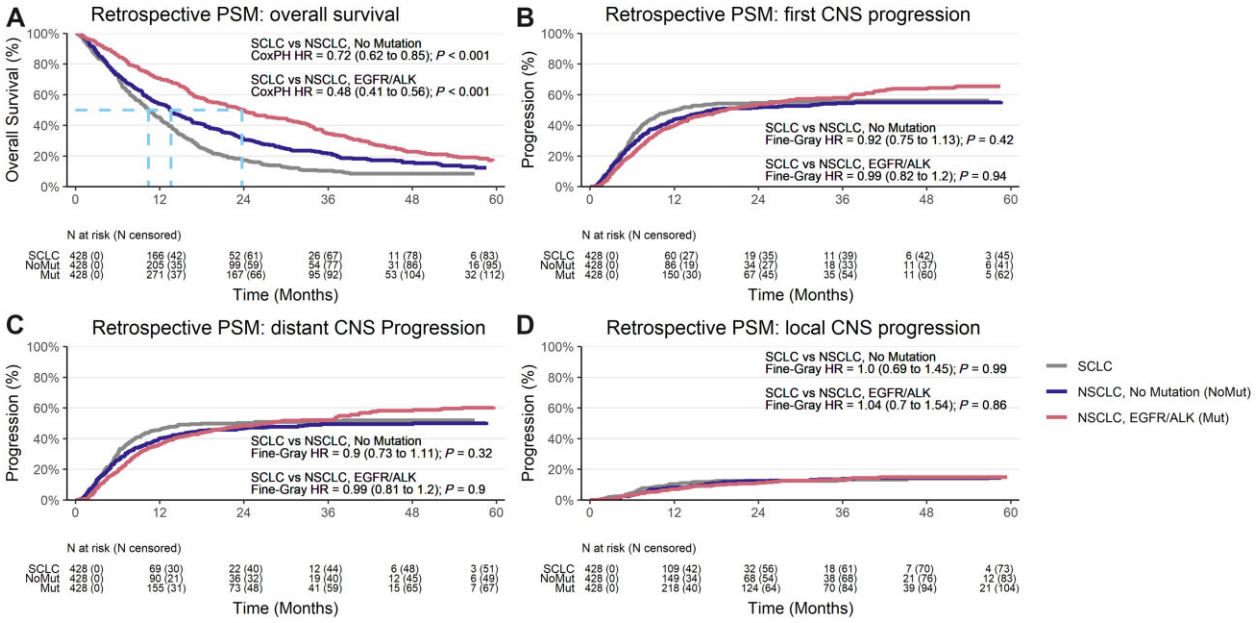

Figure 2. Propensity score-matched (PSM) analyses in the retrospective dataset with NSCLC stratified by EGFR and ALK status. **A**) Overall survival (OS). **B**) First central nervous system (CNS) progression (FCP). **C**) Distant CNS progression (DCP). **D**) Local CNS progression (LCP). Three-way (1:1:1) PSM was performed to create cohorts balanced for number of brain metastases (BrM), cumulative BrM volume, extracranial metastases, Karnofsky Performance Status, extracranial metastases, presence of BrM at diagnosis, sex, year, and region. Patient characteristics displayed in Supplementary Table 3 (available online). The hazard ratio (HR) and 95% confidence interval (CI) for overall survival analyses were modeled using Cox proportional hazard regression (CoxPH). The hazard ratio and confidence interval were modeled for CNS progression analyses using Fine-Gray models treating death as a competing risk. Small-cell lung cancer (SCLC) represents the reference (HR = 1) for the OS and CNS progression models. EGFR = Epidermal growth factor receptor; ALK = Anaplastic lymphoma kinase.

treatment strategies, including WBRT (36). Neurological mortality was uncommon overall, and no statistically significant differences between SCLC and NSCLC were observed on multivariable analyses in either the retrospective or JLGK0901 datasets. These observations challenge historical concerns for higher rates of neurological mortality after SRS specific to SCLC histology. Moreover, because cognitive and quality of life advantages with SRS alone (without WBRT) have been demonstrated in clinical trials with a median OS of 7-12 months (6-8), the observed median OS of 8.6-10.4 months for SCLC patients in this study suggests that many SCLC patients achieve survival outcomes that are sufficient to potentially benefit from a first-line SRS treatment paradigm.

Detailed CNS progression analyses demonstrated shorter time-to-event outcomes for FCP and DCP for SCLC compared with NSCLC patients in the retrospective dataset overall. Similar

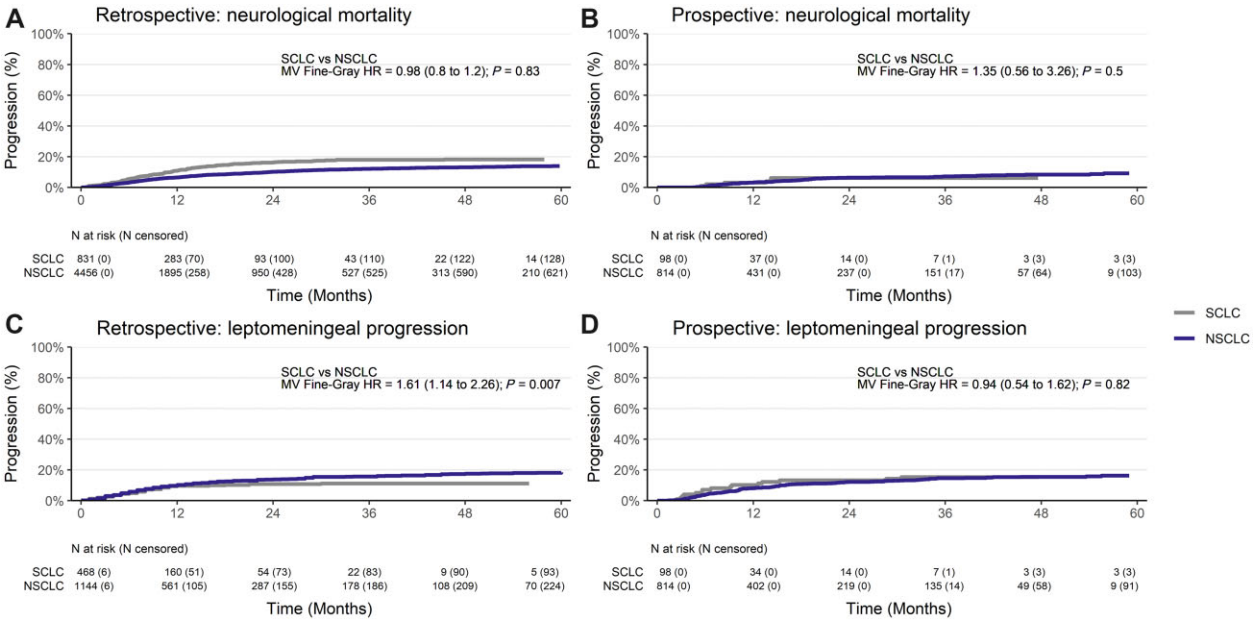

Figure 3. Neurological mortality and leptomeningeal disease (LMD) progression after first-line SRS. **A**) Retrospective dataset, neurological mortality. **B**) Japanese Leksell Gamma Knife Society (JLGK0901) (prospective dataset), neurological mortality. **C**) Retrospective dataset, LMD progression. **D**) JLGK0901, LMD progression. The hazard ratio (HR) and 95% confidence interval (CI) for overall survival analyses were modeled using multivariable Fine-Gray models treating any death as competing risk for LMD and nonneurological mortality as a competing-risk for neurological mortality. Multivariable models were adjusted for cofactors as described in the methods section.

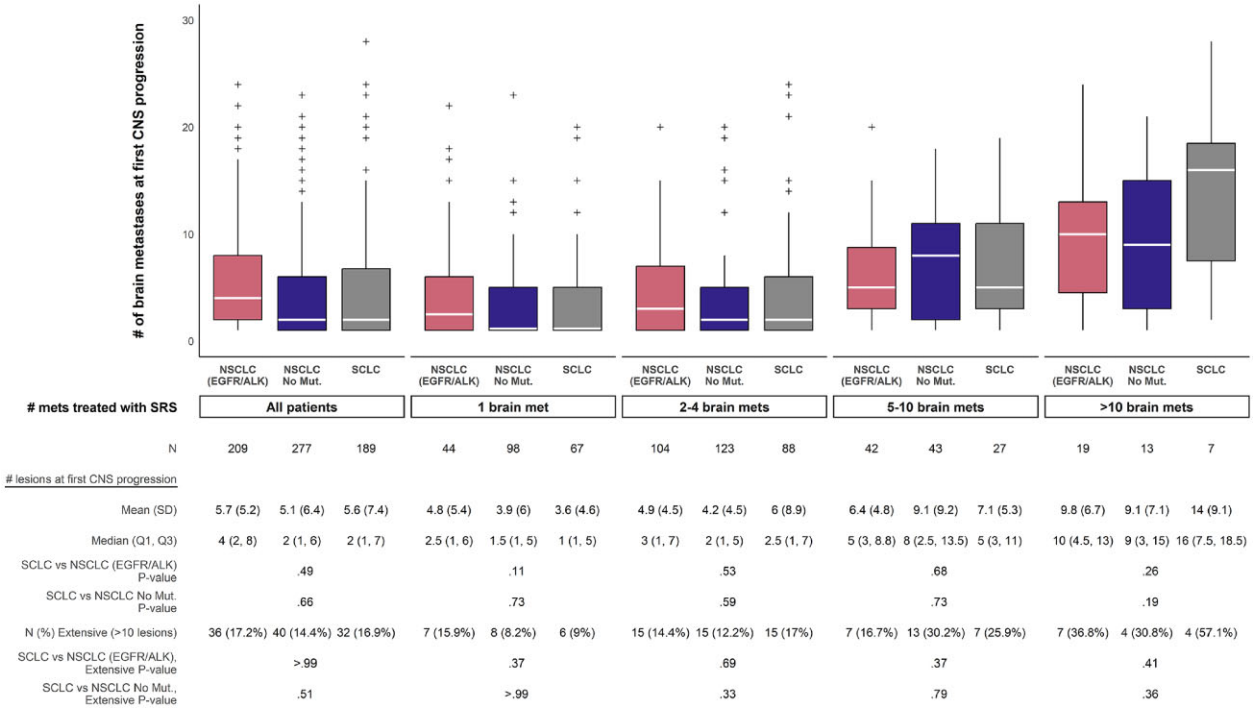

Figure 4. Number of lesions at first central nervous system (CNS) progression with non-small cell lung cancer (NSCLC) stratified by mutation status. **Horizontal lines** within the shaded boxes represent the median. **Shaded boxes** represent the interquartile range (IQR). **Vertical thin solid lines** (whiskers) extending above and below boxes represent quartile 3 + 1.5*IQR and quartile 1 − 1.5*IQR, respectively. **Crosses** above the vertical lines represent individual patient outliers. Six outliers above the y-axis are not shown due to display limitations (3 SCLC patients with 2-4 mets treated with first-line stereotactic radiosurgery (SRS) who had 32, 40, and 58 lesions at CNS progression and 3 non-mutated [no mut] NSCLC patients with 1 [n=1] and 2-4 [n=2] mets treated with first-line SRS who had 46, 33, and 50 lesions at CNS progression, respectively). The molecularly stratified analyses above were limited to patients treated in years 2005 and later as described in the methods. For statistical analyses: for comparison of all patients a log-linear regression was used and adjusted for number of lesions treated with SRS, for comparisons stratified by the number of lesions treated with SRS (1, 2-4, 5-10, >10 lesions) the Wilcoxon rank sum test was used, and for extensive (>10 lesions at CNS progression) comparisons a Fisher exact test was used. EGFR = Epidermal growth factor receptor; ALK = Anaplastic lymphoma kinase.

hazard estimates for CNS control outcomes were observed between the retrospective dataset and JLGK0901 (Table 2), but these did not reach statistical significance in JLGK0901, which may be attributable to differences in the sample sizes of the datasets. In the PSM datasets matched for baseline factors notably controlling for BrM volume, a negative prognostic factor for CNS control (37) that was higher among SCLC patients (Table 1), no statistically significant differences were observed in any CNS progression outcomes. Local control was encouraging and similar across comparisons of SCLC and NSCLC, and the predominate pattern of CNS failure was distant. Differences in the rates of FCP between SCLC and NSCLC in both the retrospective and JLGK0901 datasets tended to be larger at 12 months (9.4%-13.3%) than at 24 months (5.7%-9.5%) (Table 2), with CNS progression events plateauing during this period due to the competing risk of death. These data suggest that post-SRS SCLC progression events tend to occur earlier than in NSCLC overall, but the differences in rates of CNS progression become smaller over time and may be comparable in patients matched for baseline clinical factors.

Analyses of the number of lesions at CNS progression demonstrated no statistically significant differences between SCLC and NSCLC in number or rates of extensive (>10) BrM. These observations challenge the historical concern for substantially higher rates of diffuse CNS progression after SRS specific to SCLC histology. Limitations of the analysis of lesions at CNS progression include available data only in the retrospective dataset and missing data in a subset of patients with known CNS progression (Supplementary Table 7, available online). Although uncommon overall, salvage WBRT rates were higher for SCLC patients, which may, in part, reflect the fact that WBRT was standard for SCLC during the study period. Although no differences in LMD were observed in JLGK0901, LMD was increased for NSCLC compared to SCLC patients in the retrospective dataset. LMD was increased primarily in mutation-positive NSCLC, which is consistent with data demonstrating higher rates of LMD in EGFR-positive NSCLC patients (38). Reassuringly, there was no signal of increased SRS-related adverse events for SCLC patients in either dataset.

To our knowledge, the only prior study comparing SCLC and NSCLC outcomes after SRS was published by Serizawa et al. in 2002 (27). That analysis compared 34 SCLC and 211 NSCLC patients and reported no statistically significant differences in OS, local control, or distant brain control. Although histological comparisons are limited, 2 meta-analyses of retrospective data reported superior OS after first-line SRS over WBRT for SCLC (39,40), and randomized trials of SRS vs WBRT are ongoing (NRG-CC009 [NCT04804644], ENCEPHALON [NCT03297788]). Notably, the SCLC outcomes in the meta-analyses for OS (median 8-9 months), 12-month distant brain failure (41%-42%), and local failure (7%-22%) are consistent with the retrospective observations in this analysis. The higher rates of distant CNS progression for both SCLC and NSCLC in JLGK0901 may be attributable to the protocol of brain MRI surveillance every 3 months vs heterogenous institutional practices that represent an inherent limitation of the retrospective dataset (29).

Additional limitations of this analysis include the retrospective design and the unplanned nature of the secondary analysis of JLGK0901. Because WBRT was standard for SCLC during the study period, selection biases that differ between SCLC and NSCLC are expected, and these may be incompletely accounted for among the available cofactors. The retrospective NSCLC dataset included fewer contributing centers, which could introduce uncontrolled institution-related selection biases. Molecular data were only available for a subset of the retrospective dataset; because the timeline of ALK-NSCLC discovery to the first US Food and Drug Administration TKI approval occurred between 2007 and 2011 (41), patients with ALK-positive NSCLC before 2012 are expected to be underidentified. In the TKI-stratified analyses of JLGK0901, data were unavailable on TKIs entirely delivered before SRS, and some patients with EGFR mutations would have been analyzed in the no-TKI group and vice versa. Other than TKI receipt in JLGK0901, the analyses did not control for other systemic therapies, including chemotherapy, immunotherapy, and TKIs in the retrospective dataset that could influence OS and CNS control outcomes. In the retrospective dataset, incomplete data for endpoints including lesions at CNS progression, LMD, toxicity, and neurological mortality could introduce uncontrolled confounding. Extracranial progression data were not collected. Data were absent for other meaningful cofactors, including NSCLC mutations other than EGFR or ALK, NSCLC histologic subtypes, and programmed death ligand 1 (PD-L1) status.

Strengths of the analysis include the independent retrospective and JLGK0901 analytic cohorts, substantial sample size, international participation, granular CNS outcome data, adjustments for multiple established prognostic factors in multivariable models and matched datasets, and subgroup analyses controlling for EGFR and ALK. To our knowledge, this is also the first dedicated report of SRS outcomes for SCLC patients treated on a prospective clinical trial. Because it is not possible to randomly assign patients to a tumor histology, data from SCLC and NSCLC patients treated on the same prospective JLGK0901 study represent a high level of evidence for this comparison. Moreover, the generally consistent hazard estimates for OS and CNS-specific outcomes in the retrospective and JLGK0901 datasets support the validity of the observations.

In conclusion, this international analysis of first-line SRS characterizes SCLC outcomes in the context of NSCLC, where SRS is firmly established. After SRS, SCLC was associated with shorter OS compared with NSCLC. CNS progression occurred earlier in SCLC overall but was similar in patients matched on baseline factors. SCLC histology was not associated with increased neurological mortality, LMD, number of lesions at CNS progression, or adverse events after SRS compared to NSCLC. This analysis provides robust data addressing the historical concerns regarding SRS specific to SCLC histology. These data may better inform clinical expectations and individualized decision making for SCLC patients.

Data availability

JLGK0901 clinical trial participants were not consented to having their patient-level data shared, and individual patient data cannot be shared due to privacy and ethical restrictions. Requests for aggregate study data can be submitted to the corresponding author.

Author contributions

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Conflicts of interest

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References

1. Nabors LB, Portnow J, Ahluwalia M, et al. Central nervous system cancers, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw*. 2020;18(11):1537-1570.
2. Le Rhun E, Guckenberger M, Smits M, et al.; EANO Executive Board and ESMO Guidelines Committee. Electronic address: Clinicalguidelines@esmo.org. EANO–ESMO clinical practice

guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. ☆. *Ann Oncol*. 2021;32(11):1332-1347.
3. Vogelbaum MA, Brown PD, Messersmith H, et al. *Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline*. Oxford University Press US; 2022.
4. Wu Y-L, Planchard D, Lu S, et al. Pan-Asian adapted clinical practice guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO–ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS. *Ann Oncol*. 2019;30(2):171-210.
5. Tsao MN, Xu W, Wong RK, et al.; Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev*. 2018;1:CD003869.
6. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316(4):401-409.
7. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
8. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol*. 2013;31(1):65-72.
9. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483-2491.
10. NCCN Small Cell Lung Cancer Guidelines, Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed October 23, 2022.
11. Rusthoven CG, Camidge DR, Robin TP, et al. Radiosurgery for small-cell brain metastases: challenging the last bastion of preferential whole-brain radiotherapy delivery. *J Clin Oncol*. 2020;38(31):3587-3591.
12. Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. *JAMA Oncol*. 2020;6(7):1028-1037.
13. Cifarelli CP, Vargo JA, Fang W, et al. Role of gamma knife radiosurgery in small cell lung cancer: a multi-institutional retrospective study of the International Radiosurgery Research Foundation (IRRF). *Neurosurgery*. 2020;87(4):664-671.
14. Gjyshi O, Ludmir EB, Pezzi TA, et al. Evolving practice patterns in the use of prophylactic cranial irradiation for extensive-stage small cell lung cancer. *JAMA Network Open*. 2019;2(8):e199135-e199135.
15. Horn L, Mansfield AS, Szczęsna A, et al.; IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *New Engl J Med*. 2018;379(23):2220-2229.
16. Paz-Ares L, Dvorkin M, Chen Y, et al.; CASPIAN investigators. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939.
17. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(5):663-671.
18. Gjyshi O, Lin SH, Pezzi TA, et al. Care patterns for stereotactic radiosurgery in small cell lung cancer brain metastases. *Clin Lung Cancer*. 2022;23(2):185-190.
19. Lukas RV, Gondi V, Kamson DO, et al. State-of-the-art considerations in small cell lung cancer brain metastases. *Oncotarget*. 2017;8(41):71223-71233.
20. Ojerholm E, Alonso-Basanta M, Simone Ii CB. Stereotactic radiosurgery alone for small cell lung cancer: a neurocognitive benefit? *Radiat Oncol*. 2014;9(1):1-2.
21. Goncalves PH, Peterson SL, Vigneau FD, et al. Risk of brain metastases in patients with nonmetastatic lung cancer: analysis of the metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) data. *Cancer*. 2016;122(12):1921-1927.
22. Nussbaum ES, Djalilian HR, Cho KH, et al. Brain metastases: histology, multiplicity, surgery, and survival. *Cancer*. 1996;78(8):1781-1788.
23. Riihimäki M, Hemminki A, Fallah M, et al. Metastatic sites and survival in lung cancer. *Lung Cancer*. 2014;86(1):78-84.
24. Aupérin A, Arriagada R, Pignon J-P, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *New Engl J Med*. 1999;341(7):476-484.
25. Hirsch FR, Paulson OB, Hansen HH, et al. Intracranial metastases in small cell carcinoma of the lung prognostic aspects. *Cancer*. 1983;51(3):529-533.
26. Nugent JL, Bunn PA Jr, Matthews MJ, et al. CNS metastases in small cell bronchogenic carcinoma. Increasing frequency and changing pattern with lengthening survival. *Cancer*. 1979;44(5):1885-1893.
27. Serizawa T, Ono J, Iichi T, et al. Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non—small cell carcinoma. *J Neurosurg*. 2002;97(suppl 5):484-488.
28. Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro-Oncology*. 2017;19(11):1511-1521.
29. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. 2014;15(4):387-395.
30. Barnett GH, Linskey ME, Adler JR, et al.; Congress of Neurological Surgeons Washington Committee Stereotactic Radiosurgery Task Force. Stereotactic radiosurgery—an organized neurosurgery-sanctioned definition. *J Neurosurg*. 2007;106(1):1-5.
31. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346.
32. 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. *New Engl J Med*. 2004;350(21):2129-2139.
33. 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.
34. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci*. 2004;101(36):13306-13311.

35. Rassen JA, Shelat AA, Franklin JM, et al. Matching by propensity score in cohort studies with three treatment groups. *Epidemiology*. 2013;24(3):401-409.
36. Sperduto PW, De B, Li J, et al. Graded Prognostic Assessment (GPA) for patients with lung cancer and brain metastases: initial report of the small cell lung cancer GPA and update of the non-small cell lung cancer GPA including the effect of programmed death ligand 1 and other prognostic factors. *Int J Radiat Oncol Biol Phys*. 2022;114(1):60-74. doi: 10.1016/j.ijrobp.2022.03.020.
37. Baschnagel AM, Meyer KD, Chen PY, et al. Tumor volume as a predictor of survival and local control in patients with brain metastases treated with gamma knife surgery. *J Neurosurg*. 2013;119(5):1139-1144.
38. Cheng H, Perez-Soler R. Leptomeningeal metastases in non-small-cell lung cancer. *Lancet Oncology*. 2018;19(1):e43-e55.
39. Gaebe K, Li AY, Park A, et al. Stereotactic radiosurgery versus whole brain radiotherapy in patients with intracranial metastatic disease and small-cell lung cancer: a systematic review and meta-analysis. *Lancet Oncol*. 2022;23(7):931-939.
40. Viani G, Gouveia A, Louie A, et al. Stereotactic radiosurgery for brain metastases from small cell lung cancer without prior whole-brain radiotherapy: a meta-analysis. *Radiother Oncol*. 2021;162:45-51.
41. Shaw AT, Engelman JA. ALK in lung cancer: past, present, and future. *J Clin Oncol*. 2013;31(8):1105-1111.