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Comparative effectiveness of multi-fraction stereotactic radiosurgery for surgically resected or intact large brain metastases from non-small-cell lung cancer (NSCLC)

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ABSTRACT

Purpose: to investigate clinical outcomes in patients with large brain metastases from non-small-cell lung cancer (NSCLC) who received surgical resection and postoperative stereotactic radiosurgery or SRS alone.

Patients and Methods: Two hundred and twenty-two patients with 241 large brain metastases (2–4 cm in size) who received surgery and multi-fraction SRS (mfSRS) to the resection cavity or mfSRS alone were analyzed. For all lesions the delivered dose was 3 x 9 Gy over three consecutive days. Primary endpoint of the study was local control (LC). Secondary endpoints included early improvement of neurological deficits, changes in performance status, treatment-related toxicity, radiation-induced brain necrosis (RN), distant brain failure (DBF), and overall survival (OS). Kaplan-Meier analysis and cumulative incidence function were used for comparing the probability of failure.

Results: At a median follow-up of 13 months, median OS times and 1-year survival rates were comparable: 13.5 months and 59% for patients receiving surgery and postoperative mfSRS to the resection cavity and 15.2 months and 68% for those treated with mfSRS alone ($p = 0.2$). Median DBF did not differ significantly between groups (surgery and mfSRS,12 months; mfSRS,14 months). Eighteen patients receiving surgery and mfSRS and 17 patients treated with mfSRS alone recurred locally ($p = 0.2$); respective 6-month and 12-month LC rates were 87% and 83% and 96% and 91% ($p = 0.15$). The 1-year cumulative incidence rates of RN were 15% and 7% after postoperative mfSRS and mfSRS alone ($p = 0.03$), respectively.

Conclusions: In conclusion, mfSRS is an effective treatment for patients with large brain metastases from NSCLC resulting in equivalent LC and lower RN and risk of leptomeningeal spread compared to surgery and mf-SRS to the resection cavity. Surgery is an effective treatment option for patients with large symptomatic brain metastases who require rapid relief of neurological symptoms caused by tumor mass effect.

1. Introduction

Brain metastases from non-small cell lung cancer (NSCLC) occur in approximately one-third of patients and their presence is associated with poor prognosis, neurological deterioration, and diminished quality of life, requiring urgent treatment [1]. For these patients, surgical resection, stereotactic radiosurgery (SRS), and whole brain radiation therapy (WBRT) are the most common local treatments.

The clinical management of patients with brain metastases is changed substantially in the last years, with a shift away from WBRT to SRS. Currently, SRS alone is the recommended treatment for patients with a limited number of brain metastases, yielding an equivalent survival but lower risk of long-term neurotoxicity compared with SRS plus WBRT [2,3]. Surgical resection is often performed in patients with larger lesions and mass effect, with a reported 1-year local control of 50–60%, which is significantly increased with the use of postoperative radiation [2,4–7].

While postoperative WBRT has been traditionally used in the past,

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SRS has been increasingly used over the last years to deliver focal radiation to the resection cavity. The efficacy of postoperative SRS given in single or few fractions [2–5] has been reported in several studies [6–12]. Its superiority over surgery alone has been demonstrated in a randomized trial of 131 patients with 140 resected brain metastases who were randomly assigned to receive postoperative SRS or observation [6]. With a median overall survival (OS) of 17 months in both groups, local control (LC) rates were 72% in postoperative SRS group and 45% in observation group at 12 months ($p = 0.01$), with no additional toxicity. In another trial of 194 patients with 1–3 brain metastases < 5 cm in diameter who were randomly assigned to receive postoperative SRS or WBRT, Brown et al. [6] showed that postoperative SRS resulted in similar survival and better cognitive function and quality of life compared with adjuvant WBRT. Results of these trials suggest that postoperative SRS should be considered the new standard of care for patients with resected brain metastases; however, there are only few comparative studies on effectiveness and safety of combined surgery and SRS versus SRS alone [13,14].

In our Institution, brain metastases larger than 2.5–3 cm in size or even smaller (> 2 cm in size) if located near or in eloquent areas (ie, motor, somatosensory, speech, visual cortices, basal ganglia, thalamus, and the brainstem) are usually treated with multi-fraction SRS (mfSRS) to minimize the increased risk of late radiation-induced brain necrosis (RN) associated with high-dose, single-fraction SRS [15,16]. In a recent study of 289 patients with brain metastases > 2.0 cm in size treated with either single-fraction or multi-fraction SRS (3 x 9 Gy) at the University of Rome Sapienza, Sant' Andrea Hospital, mfSRS resulted in significantly better LC and reduced risk of RN [17].

In this study we have evaluate the clinical outcomes in patients with NSCLC who received surgery and mfSRS to the resection cavity or mfSRS alone for brain metastases.

2. Patients and methods

Between September 2011 and June 2017, 273 consecutive patients ≥ 18 years old with one to four NSCLC brain metastases who received surgical resection lesion followed by postoperative mfSRS (3 x 9 Gy) to the resection cavity or mfSRS alone for at least one metastases of 2–4 cm in size were retrospectively evaluated. For patients presenting with multiple metastases, small lesions (< 2–2.5 cm in size) were usually treated with single-fraction SRS at doses of 18–22 Gy, although data analysis was beyond the scope of this study and LC following the radiation treatment was not reported. All radiographic, surgical, and pathologic information were drawn from a prospectively maintained database of patients with brain tumors treated at Neuromed Hospital, Sant'Andrea Hospital, and UPMC Hillman Cancer Center San Pietro Hospital. Fifty-one patients were excluded for the following reasons: insufficient clinical information at follow-up (n = 17), prior WBRT (n = 16), different radiation schedules (n = 13) or incomplete resection (n = 5). Finally, a total of 222 patients with 241 brain lesions receiving mfSRS were evaluated. All patients gave their written informed consent to the treatment. All radiation treatments were performed at University of Rome, Sant'Andrea Hospital, and UPMC Hillman Cancer Center, San Pietro Hospital; the study was approved by the respective local Institutional Review Boards.

In general, patients who underwent surgery plus mfSRS received the surgical treatment as initial treatment of one or two large and/or symptomatic metastases, and were subsequently referred to our radiation oncology unit. For patients presenting with multiple brain metastases, high-risk surgical patients, or for those who refused surgery, mfSRS alone was commonly used to treat relatively large metastases (> 2.5 cm in size) or located in close proximity to critical structures (brainstem, optic pathway).

All lesions were treated with LINAC-based SRS using a commercial stereotactic mask fixation system in conjunction with the IPlan treatment planning system (Brainlab). Target volumes were contoured on thin-slice (1 mm) gadolinium-enhanced T1-weighted axial MR imaging obtained 3–7 days prior to SRS and fused to the treatment planning CT. For patients receiving surgery, the gross tumor volume (GTV) was delineated as the edge of the resection cavity, with no inclusion of surrounding areas of edema and the surgical resection corridor. To account for microscopic disease, the clinical target volume (CTV) was contoured by adding a margin of 1 mm around the resection cavity; an additional margin up to 5 mm over the craniotomy bone flap adherent to the underlying dura was added for lesions presenting with preoperative dural contact. For patients with intact metastases, the GTV was delineated as the contrast-enhancing tumor demonstrated on MRI scans without CTV expansion. For all lesions, 1 mm geometric expansion was created around the GTV to generate the planning target volume (PTV).

According to previous clinical experiences, lesions were treated with a dose of 3 x 9 Gy over three consecutive days [10,17–19]. Doses were usually prescribed to the 80% isodose line with a minimum 95% target coverage of the prescribed dose. The planned radiation dose was delivered by a linear accelerator (Varian Clinac 600 DBX or TrueBeam STx) by using dynamic conformal arc therapy or modulated arc therapy. Dexamethasone therapy was started by the first day of treatment at doses of 4 mg PO per day and generally discontinued within one week.

Patients were examined every 1–2 months. At each visit, the neurological status and the severity of complications were scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03 (NCI-CTCAE) [20]. MRI scans were performed every 2–3 months, and responses determined according to the RANO criteria [21], with tumor measurements of all scans carried out by same radiologist (A.R.) Diagnoses of tumor progression or RN were determined on the basis of histologic findings (for patients who underwent surgical resection) or by imaging using MRI and 3,4-dihydroxy-6-(18)F-fluoro-L-phenylalanine (F-DOPA) PET-CT. In summary, tumor progression was defined as any increase of lesion on postcontrast T1-weighted images in at least two subsequent MRI scans if associated with: - a cerebral blood volume ratio (rCBV) > 2.0 at dynamic susceptibility-weighted contrast-enhanced perfusion images (calculated by dividing the lesion CBV value by the mean CBV value in the normal white matter), and – maximum lesion to maximum background uptake ratio ($SUVL_{max}/Bkgr_{max}$) > 1.59 at F-DOPA PET-CT. Shrinking or stable lesions over a period of at least 6 months associated with: - a rCBV < 2.0 and – a $SUVL_{max}/Bkgr_{max}$ < 1.59 were diagnosed as RN. Following these criteria, the reported sensitivity and specificity of MRI and PET-CT are of 86.7% and 90%, and 92.3% and 68.2%, respectively [22].

2.1. Data analysis

Primary endpoint of the study was local control (LC). Secondary endpoints included early improvement of neurological deficits, changes in performance status, related-treatment toxicity, radiation-induced brain necrosis (RN), distant brain failure (DBF), and overall survival (OS).

OS was estimated using the Kaplan-Meier method from the date of the radiation treatment to the date of death from any cause or to the date of last follow-up for survivors. As censoring patients at time of death with Kaplan Meier method would lead to biased probability of LC and occurrence of RN given the high rate of death in patient population, cumulative incidence curves and Gray's test [23] were used to compare – LC accounting for either death or distant brain progression treated with WBRT or development of RN as competing risks, – DBF accounting for death as competing risk, and - development of RN accounting for death, local progression and distant brain progression treated with WBRT as competing risk. Patients who did not experience an event were censored at the time of the last follow-up.

Chi-Square and non-parametric Mann-Whitney tests were used to examine differences between groups), and the Cox proportional hazards model was employed for univariate and multivariate analysis to assess

Table 1
Patient characteristics and treatment parameters.

	Surgery and mfSRS	mfSRS alone	P value
Variable	N = 95	N = 127	
Sex (F/M)	42/53	60/71	0.8
Age (years)			0.6
median	59.4	61.1	
range	26-80	34-83	
Histology			0.2
Adenocarcinoma	75	109	
Non-adenocarcinoma	20	18	
Presence of EGFR mutations			0.8
No	77	101	
Yes	18	26	
KPS			0.5
median	80	80	
50-70	29	41	
80-100	66	86	
Extracranial metastases			0.5
Absent	22	29	
Stable	38	56	
Progressive	35	42	
Brain metastases at the time of diagnosis			0.7
No	80	105	
Yes	15	22	
Number of metastases			0.7
single	29	33	
multiple	66	94	
2 metastases	37 (2)*	26 (3)*	
3 metastases	18 (3)*	28 (5)*	
4 metastases	10 (1)*	40 (5)*	
Lung-molGPA score			0.2
0-1	15	21	
1.5 -2.0	36	50	
2.5 -3.5	30	38	
3.5-4	14	17	
Size of metastases			0.8
Median cm)	3.3	3.0	
Range (cm)	1.6-4.8	1.7-4.3	
2-3 cm	38	50	
3-4 cm	57	77	
GTV (cm^3)			0.4
median	10.8	10.3	
range	3.5 – 46.3	3.1 - 37.1	
PTV (cm^3)			0.03
median	22.4	15.6	
range	6.3-67.4	5.6 – 44.6	
Conformity index*			0.3
median	1.46	1.40	
range	1.25-2.2	1.20-2.1	

KPS, Karnofsky Performance Status; mf-SRS, multi-fraction radiosurgery.
EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic Lymphoma Kinase.
Lung-molGPA, Graded Prognostic Assessment for Lung Cancer using molecular markers; GTV, Gross Target.
PTV, Planning Target Volume.
* number of patients receiving surgery and mfSRS or mfSRS alone for two lesions.
* calculated as prescribed isodose volume/tumor volume encompassed by the prescription isodose volume.

the effects of clinical/treatment variables on clinical outcomes. Variables included in the univariate analysis were age at diagnosis, gender, KPS score, systemic therapies, number of metastases, presence of EGFR mutations, controlled (absent/stable) extracranial disease, lung-molGPA score [24], conformity index (as defined by the prescribed isodose volume/tumor volume encompassed by the prescription isodose volume), tumor size, and GTV/PTV volumes. Variables at significance levels of $p < 0.05$ were included in multivariate analysis. XLSTAT software was used for statistical analysis.

3. Results

3.1. Patient characteristics

A total of 222 consecutive patients receiving mfSRS for at least a surgically resected or intact large brain metastasis between September 2011 and June 2017 were analyzed (Table 1). Ninety-five patients who were referred to our radiation unit after complete surgical resection received postoperative mfSRS to the resection cavity and 127 patients were treated with mfSRS alone. Median time interval between surgical resection and postoperative mfSRS was 23 days (range 19–29 days). Study groups were well balanced with the exception of a greater number of patients with 3 or 4 metastases in mfSRS group and the larger PTV in the surgery and mfSRS group. One hundred and eighty-nine patients received one or two lines of therapy prior to treatments. Forty-four patients presenting with EGFR-mutated tumors received tyrosine kinase inhibitor (TKI) therapy. Among them, 20 patients received TKI therapy before the development of brain metastases, 13 before mfSRS with a median duration of 9 days (range, 1–21 days), and 7 patients after mfSRS (median 7 days; range 3–23 days).

For progressive disease, 62 patients received systemic therapy, including chemotherapy (n = 41), immunotherapy (n = 9) or molecular targeted agents (n = 11). At the time of analysis (June 2018), 43 patients were still alive (surgery and mfSRS, 20; mfSRS, 23).

3.2. Local control

With a median radiological follow-up of 12 months, eighteen patients receiving surgery and postoperative mfSRS and 17 patients treated with mfSRS alone experienced local progression ($p = 0.27$); respective cumulative LC rates were 87% (95%CI, 76–98%) and 96% (95%CI, 90–100%) at 6 months and 83% (95%CI, 74–92%) and 92% (95%CI, 85–99%) at 12 months ($p = 0.15$; Fig. 1A). Salvage therapies included surgery (n = 10), repeat SRS (n = 10), or WBRT (n = 3). In the univariate analysis, larger target volumes ($p = 0.02$) and tumor size ≥ 3 cm ($p = 0.04$) were significantly associated with higher rates of local failure.

3.3. Overall survival and distant brain failure

With a median follow-up of 13 months (27 months for alive patients), median OS was comparable: 13.5 months in patients treated with surgery and mfSRS and 15.2 months in patients receiving mfSRS ($p = 0.2$) (Fig. 1B); likewise, respective 6-month and 12-month survival probabilities were similar: 84% (95%CI, 74–95%) and 59% (95%CI, 47–71%) and 86% (95%CI, 74–98%) and 68% (95%CI, 56–80%). DBF, defined as the appearance of new parenchymal metastases, did not differ significantly between groups (Fig. 1C); 6-month and 12-month rates were 35% (95%CI, 21–49%) and 50% (95%CI, 37–63%) in patients receiving surgery and mfSRS and 26% (95%CI, 14–38%) and 46% (95%CI, 33–59%) in those having mfSRS alone. With a median time of 4 months (range 2–15 months), MRI revealed the presence of leptomeningeal disease in 6 (7%) patients who received surgery and postoperative mf-SRS and in none of patients treated with mf-SRS alone (p = 0.01). A nodular leptomeningeal enhancement contiguous to the surgical cavity (in the subarachnoid space around the craniotomy site) was seen in 2 patients and a diffuse leptomeningeal spread in 4 patients. Salvage therapies for intracranial progression included surgery (n = 14), SRS (n = 78), and WBRT (n = 28), given alone or in combination. Median survival after WBRT was 5.3 months, being similar between groups ($p = 0.4$). Forty-three patients succumbed to their intracranial disease and 141 patients died of progressive extracranial disease, with no significant differences between the groups.

In the multivariate analysis, controlled extracranial disease, EGFR-mutated tumors, a single brain metastasis, adenocarcinoma histology, and KPS > 70 emerged as significant indices of prolonged OS

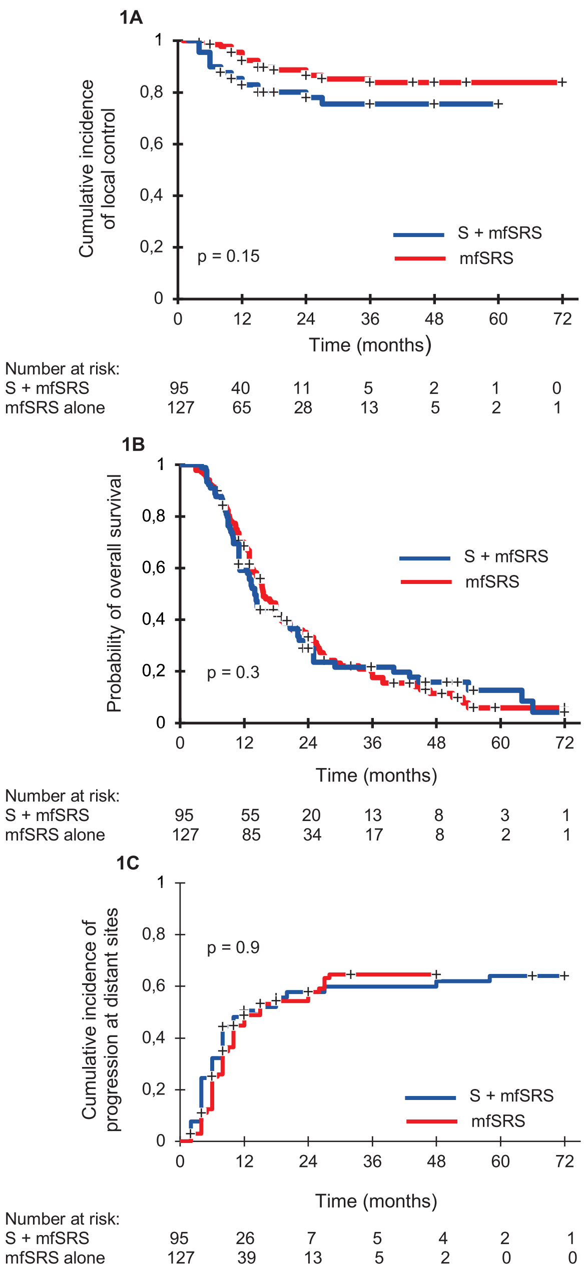

Fig. 1. Kaplan-Meier analysis of overall survival (1,A) and cumulative incidence of distant progression (1,B) and local control (1,C) for 222 patients who received surgery and multi-fraction stereotactic radiosurgery (S + mfSRS) or multi-fraction stereotactic radiosurgery alone (mfSRS). There were no statistical differences in overall survival, distant and local progression between the two groups.

(Table 2). Median survival significantly improved from 14.2 months to 23.4 months in EGFR-mutated NSCLC patients receiving TKI treatment (Fig. 2,A); OS was significantly longer in those starting treatments after being diagnosed with brain metastases (median survival, 13.2 vs 34.0 months, respectively; ($p = 0.02$)). According to the lung-molGPA score, median survival times were 7.2, 14.1, 25.7 and 39.5 months in patients with scores of 0–1, 1.5–2, 2.5–3 and 3.5–4 ($p < 0.001$), respectively, (Fig. 2,B). TKI therapy and the presence of a single metastasis were significantly associated with a decreased risk of DBF (Table 2). The impact of prognostic factors was similar between the two groups.

Table 2
Multivariate analysis of prognostic factors for OS and DBF*.

Outcome	Variable	Hazard ratio	95% CI	P
OS	Stable extracranial disease	0.51	0.34-0.85	0.01
	KPS > 70	0.61	0.47-0.94	0.03
	EGFR TKIs therapy	0.46	0.28-0.81	0.007
	Histology (ADC)	0.68	0.34-0.95	0.04
	Single brain metastasis	0.66	0.43-0.94	0.04
DBF	EGFR TKIs therapy	0.53	0.36-0.91	0.03
	Single brain metastasis	0.59	0.35-0.96	0.04

Abbreviations: OS overall survival; DBF distant brain failure; HR hazard ratio; CI confidence interval; group.
ADC, adenocarcinoma; TKI, tyrosine kinase inhibitor.
The following variables were evaluated in the univariate analysis: age, gender, KPS score, histology, EGFR-mutated tumors treated with TKI, extracranial disease status, systemic therapy, number of metastases, time to brain metasases development, conformity index, and irradiated volumes.
* Variables with a significance of $p < 0.05$ at univariate analysis were included in the multivariate analysis.

3.4. Clinical outcomes and analysis of complications

Changes in KPS score at 3 months after treatments were comparable between the two groups: KPS improved, remined stable, or worsened in 43, 35 and 17 patients receiving surgery and mfSRS, respectively, and 48, 63, and 16 patients treated with mfSRS alone, respectively ($p = 0.5$). At the same time interval, steroids dose reduction or withdrawal occurred in 59% of 95 patients undergoing surgery and mfSRS group, and 62% out of 123 patients receiving mfSRS alone ($p = 0.67$). New postoperative neurological deficits occurred in 7 (8%) patients, causing permanent moderate (n = 2) or major (1) functional impairment.

One or more neurological deficits, including focal deficits (weakness, gait disturbances, visual field defects, aphasias, and sensory deficits) and neurocognitive deficits, were present in 44 receiving surgery and mfSRS and 39 patients treated with mfSRS alone (Table 3); post-treatment neurological deficits were present in 14 and 18 patients, respectively. For patients subjected to surgery and postoperative mfSRS, neurological deficits improved in 34, remained stable in 4, and worsened in 6 patients. Amongst these six patients receiving postoperative rehabilitation, neurological deficits resolved completely (n = 3) or improved (n = 2) within 10 weeks (median 4 weeks) from surgery. In the same interval of time, neurological deficits improved in 22, remained stable in 11, and worsened in 6 patients receiving mfSRS alone (median time of 4 weeks; range 2–16 weeks). Differences in neurological improvement were statistically significant ($p = 0.04$).

KPS improved, remined stable, or worsened in 32, 4 and 8 patients receiving surgery and mfSRS, respectively, and 19, 11, and 9 patients treated with mfSRS alone, respectively ($p = 0.03$). Amongst patients with KPS score < 70, 19 (65%) of 29 patients in surgery and mfSRS group and 15 (36%) of 41 patients in mfSRS group were able to carry on normal activities ($p = 0.03$). Steroid medications were reduced or no longer used in 29 (59%) patients undergoing surgery and mfSRS group, and 17 (44%) patients receiving mfSRS alone ($p = 0.1$). Larger metastases (> 3 cm in size), and lesion located in motor cortex were significantly associated with a worsened outcome ($p = 0.043$ and $p = 0.02$).

Eighteen patients undergoing postoperative mfSRS and 13 subjected to upfront mfSRS experienced RN, as assessed by histology or MRI/PET-CT imaging (mfSRS, 8 and 5 patients; surgery and mf-SRS, 10 and 8 patients). RN was symptomatic in 19 patients (mfSRS, 7 patients; surgery and mfSRS, 12 patients); grade 2 (n = 14) or grade 3 (n = 5) toxicities included seizure (n = 4), sensory/motor deficits (n = 11), cognitive deficits (n = 4), and speech deficits (n = 5), requiring surgery (n = 8) or medical treatment (steroids or bevacizumab; n = 11).

The 1-year cumulative incidence of RN was 15% after surgery and mfSRS and 8% after mfSRS alone ($p = 0.03$); the risk of developing

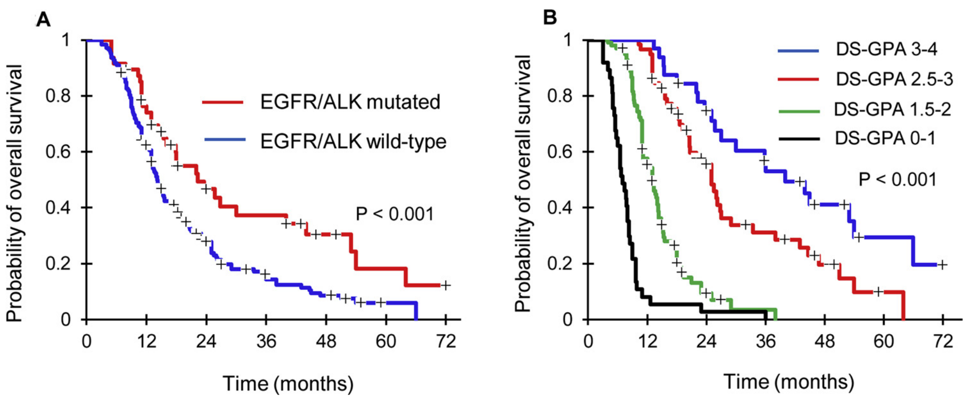

Fig. 2. Kaplan-Meier analysis of overall survival in EGFR-mutated NSCLC patients receiving TKI treatment (1,A) and according to the lung-molGPA score (1,B). Differences between groups were significant. Legend: EGFR, Epidermal Growth Factor Receptor; NSCLC, non-small-cell lung cancer; Lung-molGPA, Graded Prognostic Assessment for Lung Cancer Using Molecular Markers.

symptomatic RN was 11% and 5%, respectively, ($p = 0.025$). In univariate analysis, larger GTV ($p = 0.03$) and PTV ($p = 0.005$), and volume of normal brain irradiated with 18 Gy ($V_{18\text{-}Gy}$) ($p = 0.0003$) were associated with an increased risk of RN; in multivariate analysis, $V_{18\text{-}Gy}$ was the strongest independent prognostic factor ($p = 0.01$). With a median $V_{18\text{-}Gy}$ of 26 cm^3 for all lesions, the cumulative incidence of RN was 5% for $V_{18\text{-}Gy} \leq 26$ cm^3 and 19% for $V_{18\text{-}Gy} > 26$ cm^3 at one year ($p = 0.01$).

4. Discussion

Results of this study, where mfSRS was used for either intact or resected large NSCLC brain metastases, shows that mfSRS alone produces high LC rates consistent with those seen after complete surgical resection and postoperative mfSRS to the resection cavity, although with a significantly reduced risk of RN and leptomeningeal carcinomatosis. Specifically, 12-month LC were 92% after mfSRS and 83% after postoperative mfSRS, with respective risks of developing symptomatic RN of 5% and 11%.

Multi-fraction SRS has been increasingly used to treat large brain metastases [27–30]. Using SRS at doses of 24–35 Gy given in 3–5 fractions to either intact or resected brain metastases, retrospective studies have shown 1-year LC rates from 70% to 90%, with a variable risk of RN of 2% to 15% [10–12,17,25–28]. Currently, there is no study comparing the outcome of single- or multiple-fraction SRS to the resection cavity. In Brown et al. [6] randomized trial, cavity volumes up to 14·3 cc received single SRS doses of 17–20 Gy, whereas larger cavities received radiation doses of 12 to 15 Gy. The 6-month and 12-month estimates of resection cavity control were 80.4% and 60.5%, resulting inferior to those observed with WBRT (87.1% and 80.6%, $p =$ 0·00,068). Using similar doses of 16, 14, and 12 Gy for target volumes of ≤10 cc, 10.1–15 cc, and > 15 cc, respectively, Mahajan et al. [7] observed 12-month LC rates of 43% in patients receiving surgery alone and 72% in those receiving surgery and SRS, (HR 0.46, 95%CI 0.24-0.88, $p = 0.015$). Notably, the rate of recurrence following resection and postoperative SRS was 44% for lesions ≥ 3 cm. The apparent better control of 85% at 1 year observed in our study may, at least in part, be explained by the higher BED_{12} of our regimen as compared with BED_{12} of single doses of 12–16 Gy, as used in Brown and Mahajan studies when treating large cavities [6,7]. The efficacy of different postoperative SRS schedules in terms of LC and toxicity needs to be evaluated in prospective trials.

A few retrospective studies indicated that LC following surgery and SRS is superior to SRS alone [13,14]. In a series of 213 patients with 223 treated large brain metastases from different histologies receiving SRS alone or combined surgery and SRS, given either preoperatively or postoperatively, Prabhu et al. [14] found that surgery and SRS resulted in lower 1-year local recurrence rates (36.7% vs 20.5%; P = 007), although the treatment was associated with a higher rate of RN. Similar results have been reported in another retrospective study of 120 consecutive patients with melanoma brain metastases who received mfSRS (3 x 9 Gy) or surgery and postoperative mfSRS to the resection cavity at Rome University Sapienza; 1-year local failure rates were 28% and 12% (p = 0.02), respectively. The use of different treatment schedules and the inclusion of only "radiosensitive" NSCLC brain metastases may, at least in part, explain the different results observed in our study.

Treatments were generally well tolerated, with grade 2 or 3 toxicity occurring in 8% of patients. The 1-year risk of developing symptomatic RN was 11% in patients receiving surgery and postoperative mfSRS and 5% in those having mfSRS alone ($p = 0.025$), being consistent with previous published studies [13,14]. The increased risk of RN in these patients is likely due to differences in target volume delineation and the

Table 3
Changes in neurological status, Karnofsky performance status (KPS), and corticosteroid dosage in patients with neurological deficits receiving surgery and mfSRS to the resection cavity or mfSRS alone for one or two large brain metastases.

	Neurological deficits at baseline*			Neurological deficits after treatments		
	Whole population	surgery and mfSRS group	mfSRS group	Whole population	surgery and mfSRS group	mfSRS group
Symptoms	n = 83	n = 44	n = 39	n = 32	n = 14	n = 19
Headache	9	5	4	3	2	1
Cognitive/personality changes	16	5	11	4	1	3
Motor deficit	40	21	18	22	9	13
Language deficit	9	4	4	3	1	2
Visual problems	8	4	4	5	2	3
Nausea or vomiting	4	4	0	0	0	0
Sensory deficit	11	8	3	6	2	4
Changes in KPS (improved/stable/worsened)				51/15/17	32/4/8	19/11/9
Dosage of corticosteroids (reduced/stable/ increased)	83	44	39	37/17/19	29/7/8	19/9/11

mfSRS, multi-fraction SRS.
* multiple deficits were present in 13 patients.

use of different GTV-to-CTV margins between resected and intact brain metastases. Overall, current data confirms that mfSRS is a relatively safe treatment for patients with large metastases [10,17,25–28], at least when radiation doses of 24–35 Gy are given in 3–5 fractions corresponding to BED values of 90–127 Gy3 (α/β = 3 Gy) for late effects [18,19].

In our study, we observed a significant increased risk of leptomeningeal spread in patients receiving surgery followed by mfSRS to the resection cavity. A variable risk

ranging from 5% to 30% following SRS to the resection cavity has been reported in several studies [6–9,25,28], with the highest risk observed for large brain metastases located in posterior fossa and for breast cancer and melanoma histologies. Overall, our results confirm the increased risk of leptomeningeal spread following surgical resection of NSCLC brain metastases, supporting the use of mfSRS alone over the combined treatment for its better safety profile and similar LC.

Several prognostic factors were predictive of better clinical outcomes. In patients harboring EGFR mutations, the combination of SRS and TKI therapy was associated with significant better OS and DBF without increased toxicity. Several studies have assessed the efficacy of EGFR TKIs given alone or in combination with WBRT/SRS in patients with EGFR-mutated NSCLC brain metastases [31–36]; notably, higher efficacy has been observed with new-generation EGFR TKIs afatinib and osimertinib compared to first-generation TKIs gefitinib and erlotinib. Altough our results indicate a high clinical activity of TKI therapy given concurrently or sequentially to SRS for EGFR-mutated NSCLC brain metastases, the superiority of combined treatment versus TKIs monotherapys remains to be determined. A randomized trial of osimertinib with or without SRS for EGFR mutated NSCLC with brain metastases has been planned (ClinicalTrials.gov NCT03497767).

The current study has several limitations, owing to its retrospective nature. The presence of unmeasured baseline characteristics, such as presence of comorbidities and type of chemotherapy, may contribute to the observed differences in clinical outcomes between groups. In addition, the diagnosis of RN was made by imaging in a significant proportion of patients potentially underestimating its real incidence. Although a randomized trial would be the ideal way to compare the efficacy of different treatments, the homogeneous treatment methods and tumor characteristics in the current study provide evidence that mfSRS is an effective treatment in patients presenting with large NSCLC metastases.

In conclusion, mfSRS (3 x 9 Gy) represents an effective treatment option for patients with NSCLC brain metastases of 2–4 cm in size, with LC rates comparable to those observed with surgery and postoperative mfSRS to the resection cavity, but at lower risk of RN and leptomeningeal spread of disease. A combined approach may be considered in selected patients with large symptomatic brain metastases who require rapid relief of neurological symptoms caused by tumor mass effect.

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Competing interests

All authors declare that they have no competing interests.

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